J Bras Pneumol. 2021;47(6):e20210129
https://dx.doi.org/10.36416/1806-3756/e20210129

REVIEW ARTICLE

Malignant pleural mesothelioma: an update

Glaucia N. M. Hajj[1,2], Carolina H. Cavarson[1,2], Clóvis Antônio Lopes Pinto[3], Gabriela Venturi[1,4], João R. Navarro[4], Vladmir C. Cordeiro de Lima[2,5]

1. Instituto International de Pesquisa, A.C. Camargo Cancer Center, São Paulo (SP), Brasil.
2. Instituto Nacional de Oncogenômica e Inovação Terapêutica, São Paulo (SP), Brasil.
3. Departamento de Patologia Anatômica, A.C. Camargo Cancer Center, São Paulo (SP), Brasil.
4. BP Mirante, São Paulo (SP), Brasil.
5. Rede D'Or, São Paulo (SP), Brasil.

Submitted: 25 March 2021.
Accepted: 11 September 2021.

Study carried out in the AC Camargo Cancer Center, São Paulo, Brazil

ABSTRACT

Malignant mesotheliomas are rare types of cancers that affect the mesothelial surfaces, usually the pleura and peritoneum. They are associated with asbestos exposure, but due to a latency period of more than 30 years and difficult diagnosis, most cases are not detected until they reach advanced stages. Treatment options for this tumor type are very limited and survival ranges from 12 to 36 months. This review discusses the molecular physiopathology, current diagnosis, and latest therapeutic options for this disease.

Keywords: Pleural Mesothelioma; Treatment; Molecular Alterations.

INTRODUCTION

Malignant mesothelioma (MM) is a rare type of cancer associated with occupational or environmental asbestos exposure in 80% of cases.[1] The first case of MM associated with asbestos was reported in the USA, in 1967, due to an epidemic event of MM among miners, which helped to establish the association between asbestos exposure and the disease development. Hitherto rare, MM incidence has been increasing since the second half of the 20th century, a context in which MM has been linked to the indiscriminate use of asbestos over the last century.[2] The true extent of such worldwide MM epidemic is unknown. Currently, the greatest burden of asbestos use concentrates in Brazil, Russia, India, and China.[3]

The pleura is the most common site of MM origin (73-85%), followed by the peritoneum (7-18%).[4-6] MM predominantly affects males (male to female ratio 5:1), and the risk increases with age, with a higher prevalence in individuals >65 years of age.[7,8]

United Kingdom, Australia and New Zealand have the highest MM incidence rates, while Japan and Central European countries hold the lowest values.[9] It is estimated that between 2005 and 2050, approximately 94,000 cases of MPM and 15,000 cases of malignant peritoneal mesothelioma will have been diagnosed in the USA.[10]

Brazil is considered one of the most important producers and exporters of asbestos. MM mortality rate has steadily increased in Brazil, from 0.64 deaths per million population in 1980 to 1.18 deaths per million population in 2002. From 1980 to 2010, a total of 3,718 deaths from mesothelioma were recorded, mostly (2,180) occurring in the southeast of the country. The mortality rate between males and females was balanced, and 80.7% of deaths occurred in people older than 50 years. Nevertheless, a large number of patients remain undiagnosed, resulting in the current low MM incidence in Brazil.[11-13]

Germline mutations in cancer predisposition genes are reported in approximately 12% of MPM patients, being more common in younger patients, women, with little or no exposure to asbestos, and those with family history of cancer or individual history of cancer (melanoma, mesothelioma, breast cancer). *BAP1* is the most frequently mutated gene in this scenario, accounting for 3-7% of the cases.[14-16]

THE ROLE OF ASBESTOS IN MESOTHELIOMA PATHOGENESIS

Asbestos is the generic name of six varieties of fibrous minerals found in igneous and metamorphic rocks: Chrysotile (serpentine – white asbestos), Amosite and Actinolite (amphibole – brown asbestos), and Anthophyllite, Crocidolite, and Tremolite (blue asbestos).[14] The association between exposure to amphiboles and malignant pleural mesothelioma (MPM) is well described, and Crocidolite is considered the most oncogenic. It is believed that the thinner and longer (especially those longer than 8.0μm and wider than 0.25μm), the more dangerous the fibers, since they persist longer in the pleura, penetrate into the lungs, causing repeated tissue damage and repair, in addition to local inflammation.[17] Exposure to asbestos and other fibrous minerals can cause asbestosis, lung cancer, benign pleurisy, pleural plaques, and MPM.[18,19] In contrast, asbestos exposure is only very weakly associated with peritoneal malignant mesothelioma (33-50% of

Correspondence to: Glaucia Noeli Maroso Hajj. Centro Internacional de Pesquisa e Ensino, AC Camargo Cancer Center, R. Taguá, 440, Liberdade, CEP: 01509-010, São Paulo, SP, Brazil.
Tel.: 55 011 99113-1337. E-mail: ghajj@accamargo.org.br
Financial support: Instituto Nacional de Oncogenômica e Inovação Terapêutica (INCITO-INOTE).

patients report previous asbestos exposure) and the timing and duration of exposure do not directly correlate with disease development.[9]

Although the association between asbestos exposure and mesothelioma pathogenesis is widely accepted, a common hypothesis has not been reached to explain it. Up to 80% of MPM patients have been previously exposed to asbestos. However, the reason for only a small proportion of asbestos-exposed individuals develop MM (2-10%) remains unknown.[17] (Figure 1).

Mesothelial cells (MC) are highly susceptible to asbestos cytotoxicity, and many pathogenic events may contribute to carcinogenesis during the long latency period between asbestos exposure and tumor development.[20] MC is affected by various cellular changes induced by asbestos, such as DNA damage, cell cycle inhibition, and apoptosis.[21-24] Conversely, MC produces many inflammatory mediators in response to asbestos.[25]

The mechanisms through which inflammation affects the development of MM are not fully understood, but growing evidence has supported a link between the local and systemic inflammatory response and patient prognosis.[26] The presence of an intense and sustained systemic inflammatory response characterized by leukocyte migration and cytokine secretion promotes

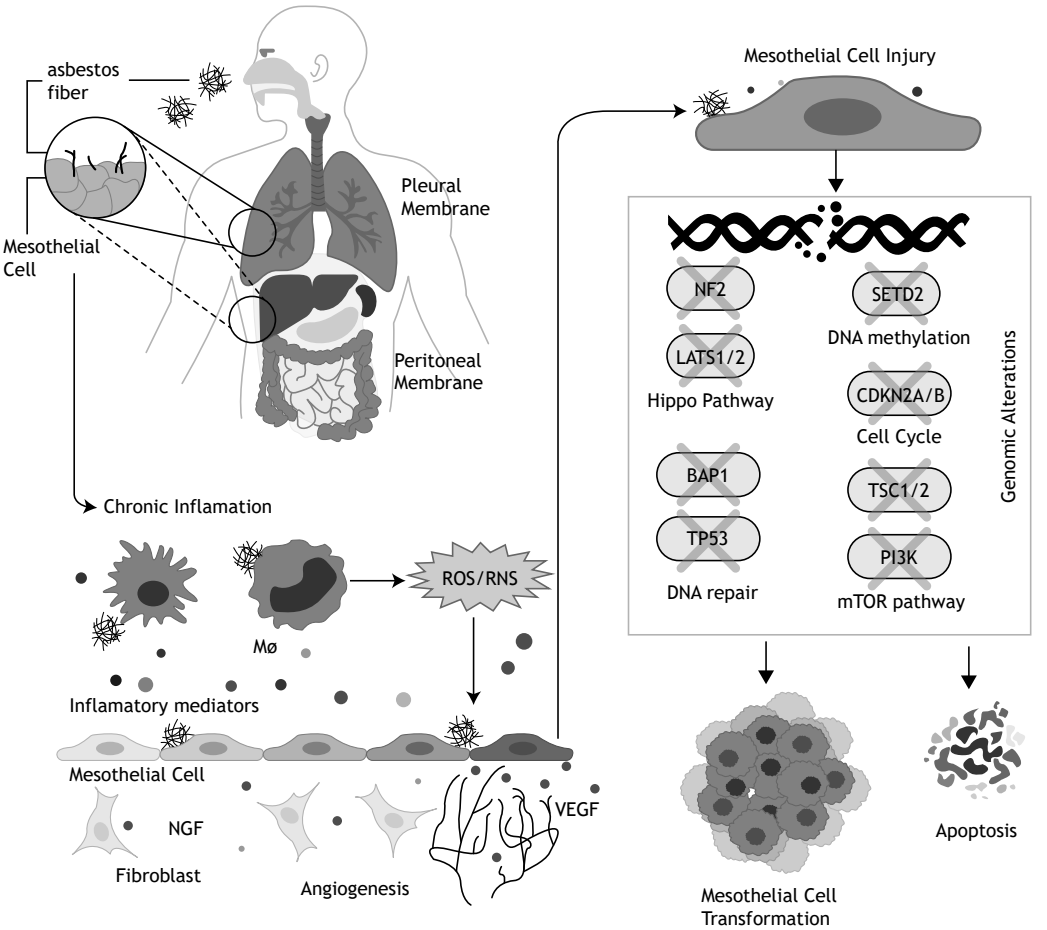

Figure 1. Molecular mechanisms associated with MM pathogenesis. Inhaled asbestos fibers transverse terminal airways and lodge themselves in the pleural space. Macrophages try to phagocytize these fibers without effect and in doing that they release reactive oxygen species and reactive nitrogen species, which may promote genotoxic damage, and recruit other inflammatory and immune cells. Repeated DNA damage by ROS and RNS may lead to the accumulation of oncogenic mutations in the mesothelial cells. The genes most frequently mutated in mesothelioma and that may be associated with malignant transformation of mesothelial cells are involved with DNA repair, the Hippo pathway, cell cycle control, DNA methylation and the mTOR pathway. Germ line mutations in genes associated with DNA repair (*BAP1, BRCA1, CHECK2*, etc) are found in 12% of mesothelioma patients and are associated with earlier disease onset and good prognosis. In parallel, the inflammatory mediators released in the microenvironment may promote cell survival (inhibiting apoptotic signals) and stimulate mesothelial cell proliferation (even in the presence of DNA damage), activate fibroblast to produce extracellular matrix proteins, and promote neoagiogenesis. These modifications favor tumor growth and create an immunossupressive milieu. Mø-macrophages; ROS-reactive oxygen species; RNS-reactive nitrogen species; NGF-neurotrophic growth factor; VEGF-vascular endothelial growth factor. Created with BioRender.com.

malignant transformation of MC.[27,28] Malignant cells attract myeloid-derived supressor cells (MDSCs), tumor associated macrophages (TAMs), and regulatory lymphocytes (Treg). These cells potentiate tumor development and promote immune escape, extracellular matrix remodeling, and angiogenesis[29,30] (Figure 1).

Tumor necrosis factor-alpha (TNFA) and nuclear factor-kB (NF-kB) signaling were also involved in MC response to asbestos. Crocidolite causes the accumulation of macrophages in the pleura and lung, which, in turn, release TNFA. Crocidolite also induces MC to express the TNFA receptor, TNF-R1, as well as to secrete TNFA (thus causing paracrine and autocrine responses).[31] The activation of the NF-kB pathway by TNFA allows MCs bearing asbestos-induced DNA damage to eventually evolve into MM. In fact, by causing the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS), whose production is catalyzed by iron, asbestos fibers can induce genotoxicity indirectly, which may lead to a wide spectrum of mutations.[32] Therefore, part of the pathogenetic mechanism of asbestos fibers is thought to be associated with their persistence in the pleura over long periods of time triggering repeated cycles of lesion/repair at the inflammation site.[33-35] Indeed, the presence of inflammatory cells in the tumor is a prognostic factor[26,36-39] (Figure 1).

MPM CLINICAL PRESENTATION, DIAGNOSIS, AND CLASSIFICATION

The latency period between the first exposure to asbestos and the diagnosis of MM is about 30 years. The unavailability of an effective screening method to detect the disease at an early stage hampers its diagnosis.[40] In turn, the diagnosis is followed by survival ranges between 12 and 30 months for localized disease, and between 8 and 14 months in advanced disease.[41,42] Most newly diagnosed patients have advanced disease, and first-line therapy prolongs survival by an average of about three months.[8,43]

The most common clinical manifestation of MPM is progressive dyspnea, usually secondary to pleural effusion formation, associated or not with non-pleuritic chest pain caused by chest wall invasion. Non-productive cough, fever, asthenia, hypoxia, weight loss, or night sweats may also be present. The disease is usually unilateral (95%) and predominantly localized to the right hemithorax (60%). Symptoms usually manifest insidiously and for a long period of time from the initial presentation to diagnosis (3 to 6 months), eventually leading to diagnosis at an advanced stage.[14,43]

Diagnosis depends on the integration of clinical presentation, imaging, and pathology. Specifically, pleural effusion appears on physical examination or chest radiography in up to 95% of cases, but its volume decreases with disease progression. The presence of chest pain or a palpable mass suggests invasion of the chest wall and portends surgical inoperability. Thoracic tomography, as well as thoracic magnetic resonance imaging, allows visualization of pleural effusion, the presence of pleural masses, and assessment of the hilar and mediastinal lymph nodes. However, magnetic resonance imaging is a more sensitive method and should be considered in potentially resectable cases.[43] In turn, PET-CT (positron emission tomography-computed tomography) is useful for detecting lymph node involvement, contralateral thoracic involvement, and distant metastases.[14,44] Figure 2 shows representative images of MPM.

The 2015 classification of WHO divides MM into epithelioid (60-80%), biphasic (10-15%), and sarcomatoid subtypes (10%), with desmoplastic (2%) features recognized in the sarcomatoid subtype. In some cases, classification can be difficult due to the presence of mixed populations.[45,46]

Epithelioid mesotheliomas have architectural, cytologic, and stromal features that allow a variety of differential diagnoses with other neoplasms. In epithelioid mesotheliomas, nuclear atypia and necrosis are independent prognostic factors, allowing the classification of epithelioid mesotheliomas into low and high histologic grades (Figure 3).[47,48]

In sarcomatoid mesotheliomas, the cells are spindly and distributed in fascicles or in a disorganized architectural arrangement, showing mild to severe cytologic atypia, in addition to the possibily of having heterologous elements. Biphasic mesothelioma must contain at least 10% of epithelioid and sarcomatoid components each, whereas desmoplastic mesothelioma must have at least 50% hyalinized fibrous stroma. Patients with sarcomatoid and biphasic tumors have significantly worse survival than those with epithelioid mesothelioma.[49]

Pleural fluid cytology allows MPM diagnosis in up to 1/3 of cases. However, the diagnosis is limited to epithelioid subtype because the sarcomatoid variant does not desquamate into the pleural space. Fine needle aspiration biopsy (FNAB) provides an accuracy of approximately 30%.[50] Unguided pleural biopsy increases the accuracy of FNAB; however, computed tomography-guided pleural biopsy is more sensitive and can establish the diagnosis in ~87% of the cases.[43] The use of video-assisted thoracoscopy/pleuroscopy has an accuracy ≥95% and is the ideal diagnostic method.[51]

Histopathological diagnosis of mesothelial lesions imply significant challenges, including differentiation of malignant lesions from benign tumors and reactive mesothelial hyperplasia or reactive fibrous pleurisy. In pleural biopsies, it can be difficult to differentiate between reactive hyperplastic mesothelium and mesothelioma, as both situations involve cytologic atypia, increased cellularity, and mitosis. Infiltration features, vascular pattern, growth pattern, extent of necrosis, and characteristics of the papillae are

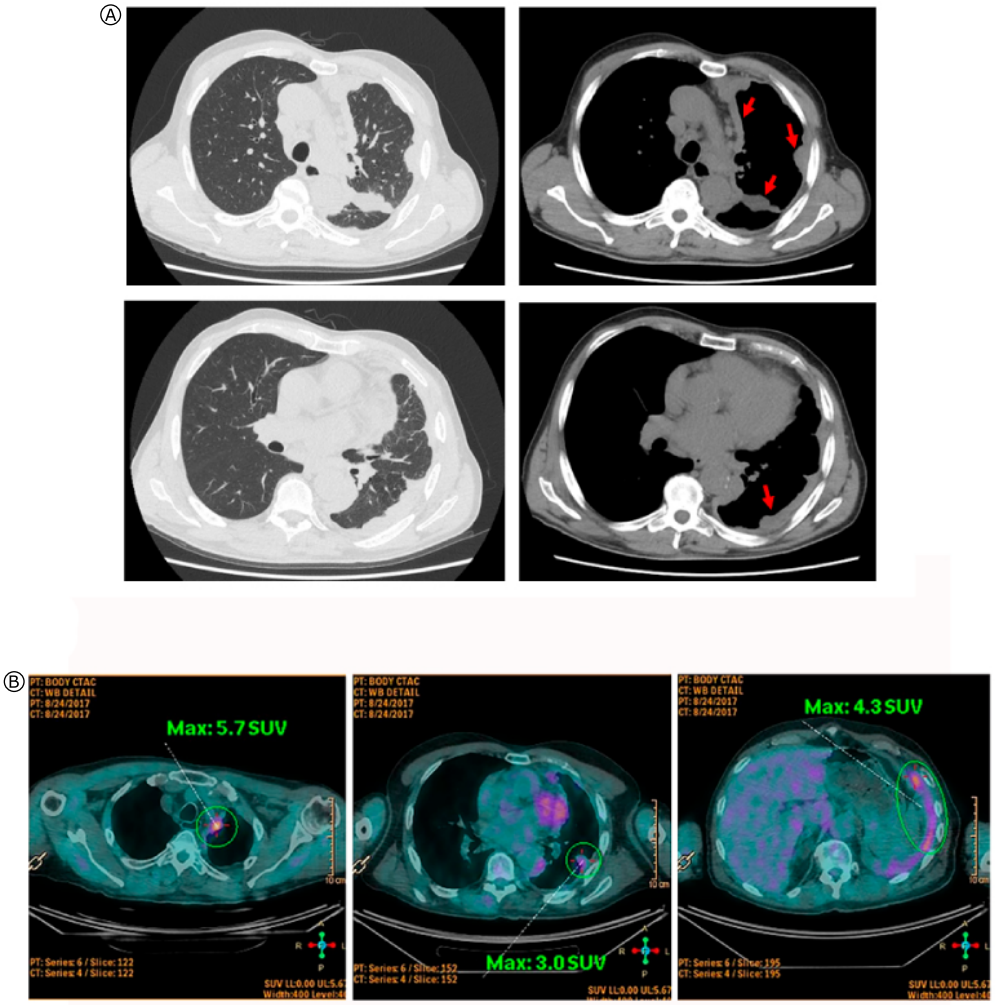

Figure 2. Representative images of the thorax from a male patient diagnosed with biphasic pleural malignant mesothelioma. (A) CT scan showing multiples areas on pleural thickening in the fissure, as well as in mediastinal and parietal pleura, sometimes forming pleural nodules, can be seen in the left hemithorax (red small arrows); (B) 18-FDG PET-CT scan showing various areas of hypermetabolic (glucose avid) tissue in the pleura can be observed on the left hemithorax.

important criteria that cannot always be evaluated in biopsies. Recently, loss of BAP1 (BRCA1-associated protein-1) expression by IHC, homozygous deletion of CDKN2A (p16) by FISH, and expression of methylthio-adenosine phosphorylase (MTAP) by IHC were added as markers to distinguish non-neoplastic from neoplastic cells when mesothelial proliferation is confined to the serosal surface. This may contribute to the differential diagnosis of reactive mesothelial hyperplasia and *in situ* malignant mesothelioma, as well as reactive mesothelial proliferations (pleurisy) that may extend to the stroma and simulate infiltrative mesothelioma.[52,53] Nuclear expression of the BAP1 protein is preserved in reactive mesothelial cells. In epithelioid mesothelioma, complete loss of expression of BAP1 and deletion of *CDKN2A* are present in up to 70% of cases.[50]

This is complicated because the MPM morphologic patterns can simulate a variety of epithelial and nonepithelial malignancies, including carcinomas, sarcomas, melanomas, lymphomas, among others.[50] Immunohistochemistry (IHC) is crucial to differentiate these entities.[52] However, no single IHC marker is sufficiently sensitive or specific to identify MPM; therefore, the use of panels consisting of at least two carcinoma markers (e.g., pCEA BER -EP4, MOC -31, Claudin 4, HEG1) and two mesothelial markers (i.e., WT1, calretinin, CK5/6, D2-40) is recommended[45,50] (Table 1).

Pleural adenomatoid tumor presents as a solitary, noninfiltrative nodule, which may contribute to the differential diagnosis with adenomatoid/microcystic mesothelioma. Somatic mutation of *TRAF7* and preservation of BAP1 favor the diagnosis of an adenomatoid tumor.[55]

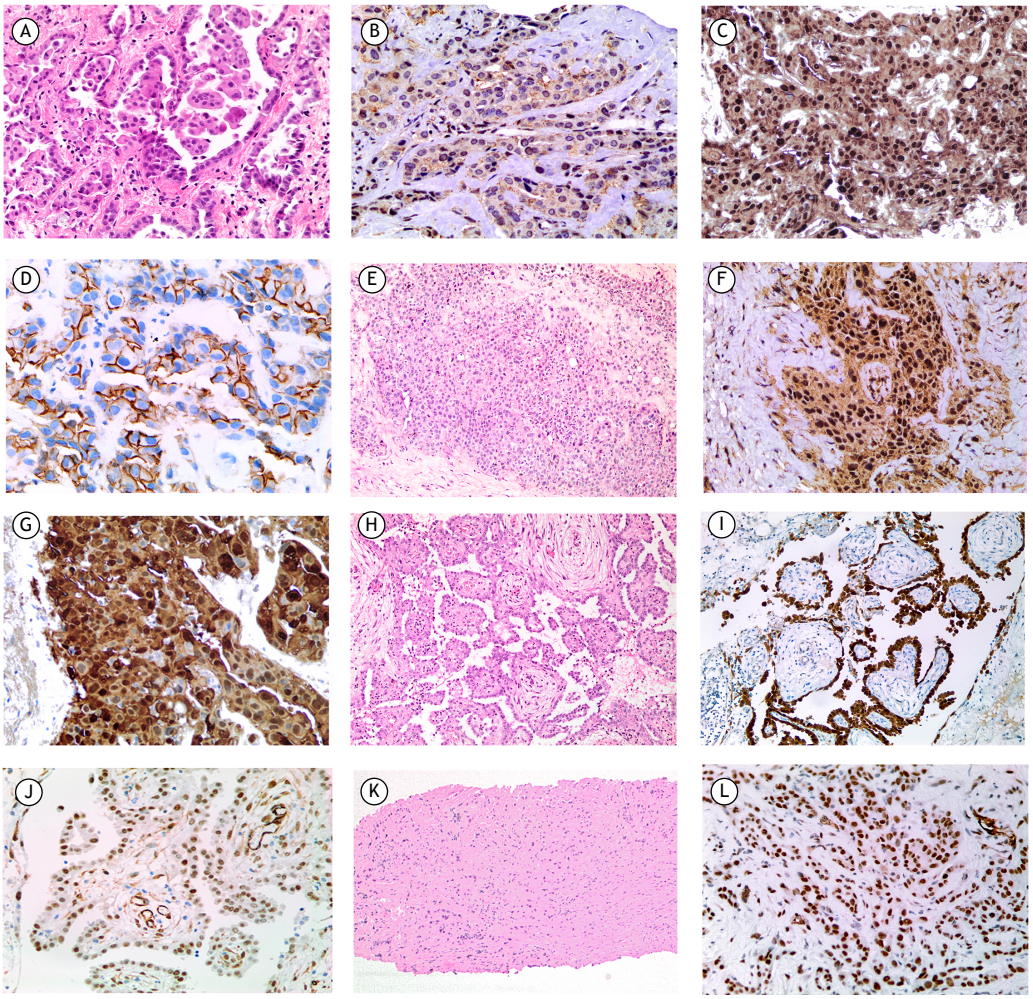

Figure 3. Photomicrographs of MPM. (A-D) epithelioid mesothelioma. (A) H&E staining showing atypical mesothelial cells arranged in papillary and tubulo-glandular patterns amid loose connective tissue. 200x; (B) loss of BAP1 expression in the nucleus of tumor cells, DAB IHC, 200x; (C) calretinin expression in tumor cells cytoplasm, DAB IHC, 200x; (D) D2-40 expression in tumor cells membranes; (E-G) Pleomorphic/solid epithelioid MPM; (E) H&E staining, 100x; (F) BAP1 expression in the nucleus of tumor cells, DAB IHC, 200x; (G) calretinin expression in tumor cells cytoplasm; (H-J) Papillary MPM. H) H&E staining showing a monolayer of mesothelial cells with low grade nuclear atypia covering a fibrovascular core, 100x; (I) calretinin expression in the nucleus and cytoplasm of tumor cells, DAB IHC, 100x; (J) WT1 expression in the nucleus of tumor cells, DAB IHC, 200x; (K-L) Desmoplastic MPM; (K) H&E staining showing isolated round and spindled mesothelial cells amidst a dense desmoplastic stroma, 40x; (L) WT1 expression in the nucleus of tumor cells., DAB IHC, 200x. DAB- 3,3'-diamino-benzidine. H&E- hematoxylin and eosin. IHC-immunohistochemistry.

Table 1. Immunohistochemical markers for diagnosis and differentiation of MM.

Mesothelial markers	Sensitivity	Specificity *versus* Lung adenocarcinoma
Calretinin	> 90%	90-95%
CK5/6	75-100%	80-90%
WT1	70-95%	~100%
D2-40	90-100%	85%
Adenocarcinoma (epithelial markers)	**Sensitivity**	**Specificity *versus* Malignant mesothelioma**
MOC31	95-100%	85-98%
BerEP4	95-100%	74-87%
BG8 (Lewis Y)	90-100%	93-97%
B72.3	25-85%	> 95%

Source: Henderson et al.[54]

For the diagnosis of metastatic carcinomas, it is recommended to add specific antibodies for primary sites, such as lung adenocarcinomas (TTF-1, napsin A), squamous cell carcinomas (p63, p40), renal cell carcinomas (PAX-8, CAIX), colorectal adenocarcinomas (CDX2), and prostate adenocarcinomas (PSA, NKX.3), in addition to the IHC panel described above. The GATA-3 antibody expressed in breast carcinomas and urothelial carcinomas may also be positive in mesotheliomas. Metastatic melanomas will express S-100, Melan-A, HMB-45, and SOX-10. Epithelioid vascular tumors (hemangioendothelioma and angiosarcoma) express CD34, CD31, and ERG, which are usually absent in mesotheliomas. A solitary pleural tumor may mimic sarcomatoid mesothelioma, nevertheless, they satin for STAT6 and CD34, and bear *NAB2-STAT6* gene fusion. In the differential diagnosis of sarcomatoid and biphasic mesothelioma with synovial sarcoma (monophasic and biphasic), molecular testing is recommended to look for *SYT-SSX1* or *SYT-SSX2* fusions, as both have nuclear labeling for TLE1. It can be challenging to establish a differential IHC diagnosis between sarcomatoid mesothelioma and primary sarcoma of the chest wall or metastases of sarcoma to the pleura, especially when heterologous components are present in the mesothelioma.[50,56] Figure 3 shows representative photomicrographs of MPM.

MOLECULAR PATHWAYS OF MM

Genomic alterations

Understanding the molecular mechanisms associated with the development of MM (Table 2) began with conventional cytogenetics and comparative genomic hybridization (CGH) analyses, which showed numerical alterations in all chromosomes, indicating that losses were more common than gains.[85,86] These studies have revealed a complex pattern of chromosomal aberrations in MPM and suggest that gene copy number alterations (CNA) are a major mechanism of carcinogenesis in this disease.[87] Multiple sites of chromosomal loss have been observed in 1p, 3p, 4, 6q, 9p, 11q, 13q, 14q, 15q, 17p, 18q, and 22q,[64,65,86,87] suggesting the involvement of tumor suppressor genes in deleted regions. Although less common, chromosomal gains of 5p, 7p, 8q, 12p, 17q, and 18q have also been documented.[88]

Commonly deleted loci include those containing tumor suppressors *CDKN2A* (cyclin-dependent kinase inhibitor 2A), located on 9p21.3,[57] *NF2* (neurofibromin 2), on 22q12,[59,60] *BAP1*(BRCA1-associated protein-1), located on 3p21.3,[67,89] and *TP53*, on 17p13. CDKN2A, encoding p16-INK4 and ARF, is the most frequently inactivated tumor suppressor gene in MM, with an incidence of homozygous deletion of 50%.[57,58,77] Loss of *CDKN2A* is associated with nonepithelial histology[90] and poorer survival.[64,91,92] *NF2* encodes the protein Merlin,[59] a transcriptional co-activator associated with ubiquitin ligase complexes and the Hippo pathway.[93,94]

Approximately 20-40% of MM have deletions or mutations in *BAP1*[67,77,78][67,77,78] and germline mutations in this gene increase the risk of mesothelioma development.[89] In mouse models, inactivation of only one *BAP1* allele increases asbestos tumorigenicity.[89] *TP53* mutations are present in approximately 8% of MM. Although this incidence is much lower than in other tumor types,[77] it is important to emphasize that *CDKN2A*, which encodes ARF and reduces MDM2 expression, is often lost. Therefore, deletion of CDKN2A results in an increase in MDM2 expression, which triggers ubiquitination and degradation of p53.[95,96] Thus, the phenotype of decreased p53 expression due to *CDKN2A* is similar to that of *TP53* mutation. Indeed, animal models heterozygous for *TP53* develop MM more rapidly when exposed to asbestos.[97]

No oncogene has yet been identified in MM, suggesting that MM is a malignancy resulting from inhibition of tumor suppressors rather than transformation by activation of oncogenes.[98]

The advancement of next-generation sequencing allowed several groups to provide a comprehensive analysis of molecular alterations in MM, which not only confirmed the previously found CNA but showed that the same genes also have common point mutations.[69,99,100]

Bueno et al.[77] published an analysis of 95 MM that confirmed previous findings of tumor suppressor genes CNAs (e.g., *BAP1, NF2, CDKN2B*, and *TP53*). In addition, newly identified mutations were described in genes that include histone modifiers such as *SETD2, SETDB1*, and *SETD5*, members of the RNA helicase family *DDX3X* and *DDX51*, a target of negative mTOR regulation *ULK2*, and a calcium channel component *RYR2*.

In another landmark study of 74 MM samples, TCGA reported deletion of *CDKN2A* and loss of *NF2* by deletion or mutation. *CDKN2A* deletions often encompass *MTAP*, which encodes methylthioadenosine phosphorylase.[81] Loss of *CDKN2A* was strongly associated with shorter overall survival and non-epithelioid histology.[64,90-92]

Two studies, involving 42 patients[73], and a larger cohort of 266 patients[84] employed targeted sequencing of key mutant MPM genes (including *BAP1, NF2, TP53, SETD2, LATS2*, and the *TERT* promoter). A molecular classification into epithelioid and sarcomatoid groups was proposed, with *BAP1* alterations found preferentially in the epithelioid group, whereas alterations in *TP53* and *LATS2* were mostly present among the sarcomatoid subtype.[84]

In addition to the highly consistent alterations in tumor suppressor genes, rarer genetic alterations have also been described. For example, activating mutations in the canonical MAPK or PI3K/AKT pathways were reported in two cohorts,[70,101] but were not identified in the TCGA cohort.[81] Recurrent novel amplification of *RASSF7* was observed in a series of 121 patients and, together with alterations in other genes from the Hippo pathway (*NF2, LATS1,* and *LATS2*), suggests a significant contribution of this pathway to tumorigenic processes.[83]

Table 2. Genomic alterations associated with MM.

Ref	Number of cases/ samples	Techniques used	Main findings
Cheng et al.[57]	40 cell lines and 23 primary tumors	Southern Blot and Targeted Seq of p16	Homozygous deletions on p16-INK in 85% both cell lines and 23% of tumors
Xio et al.[58]	50 primary tumors	FISH for p15 and p16.	Co-deletion of p15 and p16 in 72% of cases.
Sekido et al.[59]	14 cell lines and 10 primary tumors	SSCP and Southern Blot for NF2	*NF2* mutations in 41% of cases.
Bianchi et al.[60]	15 cell lines and 7 primary tumors	SSCP; Targeted Seq for NF2	*NF2* mutations in 53% of cases.
Björkqvist et al.[61]	34 primary tumors	CGH array; Southern Blot.	loss in 4q, 6q and 14q and gain in 15q and 7p
Prins et al.[62]	12 cell lines	PCR; FISH	Chromosome 9 deletion including *CDKN2A* but not *CDKN2B*.
Taniguchi et al.[63]	17 primary tumors and 9 cell lines	CGH array; Southern Blot; Targeted Seq of NF2;	Gains in 1q, 5p, 7p, 8q24 and 20p; Loss in 1p36.33, 1p36.1, 1p21.3, 3p21.3, 4q22, 6q25, 9p21.3, 10p, 13q33.2, 14q32.13, 18q and 22q.
Ivanov et al.[64]	22 primary tumors	CNA array	Deletions in 22q12.2, 19q13.32 and 17p13.1 in 55-74% and gain in 5p, 18q, 8q and 17q in 23-55% of cases.
Cheung et al.[65]	22 cell lines	CNA array	deletions of CDKN2A/ARF and CDKN2B, 1p36, 1p22, 3p21-22, 4q13-34, 11q23, 13q12-13, 14q32, 15q15, 18q12 and 22q12 in 55-90%
Takeda et al.[66]	40 primary tumors	9p21 FISH	9p21 deletion in 35 of 40 cases (88%)
Bott et al.[67]	53 primary tumors	CGH array, FISH; Targeted Seq.	Deletions at 9p21, 22q and 3p21. Mutations in BAP1, NF2, LATS1
Yoshikawa et al. [68]	23 primary tumors	Targeted Seq of BAP1	biallelic BAP1 gene alterations in 14 of 23 MMs (61%)
Guo et al.[69]	22 primary tumors	Whole-exome Seq	Major changes in copy numbers: *BAP1*, *NF2*, *CDKN2A*, *CUL1*.
Lo Iacono et al.[70]	123 primary tumors	Targeted NGS of 52 genes	Alterations in p53/DNA repair (TP53, SMACB1, and BAP1) and PI3K-AKT pathways (PDGFRA, KIT, KDR, HRAS, PIK3CA, STK11, and NF2).
Nasu et al.[71]	22 primary tumors	Targeted BAP1 Sanger Seq.; MLPA	alteration of BAP1 in 63.6% of cases
Borczuk et al.[72]	48 peritoneal and 41 pleural tumors	CNA array	Loss in BAP1, CDKN2A and NF2 in both tumor sites. Copy number gain were more common in peritoneum, loss were more common in pleura
Kato et al.[73]	42 primary tumors	Targeted NGS of 236 genes	Alterations in *BAP1* (47,6%), *NF2* (38,1%) and *CDKN2A/B* (35,7%).
Kang et al.[74]	78 primary tumors	Targeted Seq of SETDB1	Mutations in 7 patients
Ugurluer et al.[75]	11 primary tumors	Targeted NGS of 236 mutations	Mutations in 86% of pleural and 50% of peritoneal cases. Most mutated genes were BAP1 (36%), CDKNA2A/B (27%) and NF2 (27%).
Chirac et al.[76]	33 peritoneal primary tumors	CGH array	Genomic pattern similar to pleural mesothelioma: loss of 3p21, 9p21, and 22q12. novel CNA included 15q26.2 and 8p11.22

Table 2. Continued...

Ref	Number of cases/ samples	Techniques used	Main findings
Bueno et al.[77]	216 primary tumors	Whole Exome Seq, Targeted NGS	BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, CFAP45, SETDB1 and DDX51 significantly mutated genes. Gene fusion and splice alterations in NF2, BAP1 and SETD2. Alterations in Hippo, mTOR, histone methylation, RNA helicase and p53 signaling pathways.
Yoshikawa et al.[78]	33 primary tumors	CGH array for the 3p21 region; Targeted NGS of 4 genes	biallelic gene inactivation in SETD2 (9 of 33, 27%), BAP1 (16 of 33, 48%), PBRM1 (5 of 33, 15%), and SMARCC1 (2 of 33, 6%)
Desmeules et al.[79]	25 primary tumors	FISH	Identification of a *EWSR1/ FUS-ATF1* gene fusion in 4 cases
Hung et al.[80]	88 peritoneal primary tumors	FISH; Targeted NGS for ALK	ALK rearrangements in 3 cases with ATG16L1, STRN, and TPM1
Kim et al.[9]	13 peritoneal primary tumors	Targeted NGS of 510 genes;	Bi-allelic inactivation of BAP1 (9/13 cases), mutation in *NF2 (3/13)*; *SETD2 (2/13)* e *DDX3X (2/13)*.
Hmeljak et al.[81]	74 primary tumors	Whole Exome Seq.; CNA array	Inactivating alterations by mutation and CNA in: BAP1, CDKN2A, NF2, TP53, LATS2, and SETD2. Novel molecular subtype (3% of cases) genomic near-haploidization and TP53 and SETDB1 mutations
Hassan et al.[82]	239 genomic DNA from MM patients	Targeted NGS of 73 genes	12% of cases had germline mutations: 16 in BAP1 and 12 distributed among CHEK2, PALB2, BRCA2, MLH1, POT1, TP53, and MRE11A
Nastase et al.[83]	121 primary tumors	CNA array, Whole Exome Seq.;	CDKN2A deletion in 60% of tumours; BAP1 mutated or deleted in 54%; RASSF7 amplification in 33%; RB1 deleted or mutated in 26%; NF2 mutated in 20%; TP53 mutated in 8%; SETD2 in 6%; DDX3X in 5% and LATS2 in 5%.
Quetel et al.[84]	266 primary tumors	Targeted NGS 21 genes	TERT promoter, *NF2*, and *TP53* mutations associated w/ worse survival.

BAP1

Although the risk of developing MM is much higher among workers of the asbestos industry,[102] not all exposed workers develop the disease. This prompted to the search for genetic factors that predispose to MM, especially in families with multiple affected individuals,[103] which led to the identification of *BAP1* gene role.

BAP1 is an enzyme of the c-terminal hydrolase family with pleiotropic activities found in DNA repair complexes associated with BRCA1 and functions as a de-ubiquitinase.[104-106] Expression of BAP1 is associated with reduced tumor growth in several experimental models and interacts with cell cycle regulatory proteins.[107] In addition, BAP1 forms several nuclear complexes that can regulate gene transcription. Therefore, BAP1 is expected to affect a variety of cellular functions, such as chromatin remodeling, cell cycle progression, cell differentiation, and DNA repair. The BAP1 protein is also known to play an important role as an apoptosis inhibitor caused by metabolic stress.[108]

Deletions or mutations in BAP1 have been described in approximately 60% of MM,[67,68,70,71,77,78,81] with nearly 85% of peritoneal tumors having BAP1 alterations, comparing with only 20-30% of pleural tumors.[109] BAP1 is also consistently inactivated in

clear cell renal carcinomas, uveal melanomas, and cholangiocarcinomas.[110] Most mutations in BAP1 are frameshift or missense, resulting in loss of protein expression.[67,77,78] Accordingly, loss of BAP1 protein expression can be identified by immunostaining of tumor tissue, which is observed in approximately 60% of the cases.[71] Loss of protein expression is observed in approximately 60% of the cases.[111] Despite its high prevalence, loss of BAP1 expression has not been shown to affect overall survival,[71] but has been indicated to affect response to chemotherapy.[107]

Point mutations are also present in *BAP1* and can lead to amino acid substitution, whose effect on protein activity is not always obvious. For example, mutations I47F, F81V, A95D, and G178V lead to loss of protein stability and amyloid aggregation.[112] On the other hand, mutations such as A95D, Y724X, and 10 F679LfsX37 lead to a change in subcellular location from nuclear to cytoplasmic.[113]

Germline mutations in *BAP1* are associated with a highly penetrant syndrome of MM. The so-called BAP1 tumor predisposition syndrome (BAP1-TPDS) was identified by three independent research groups investigating MM, cutaneous melanoma, and uveal melanoma. Later, other tumor types such as cholangiocarcinoma, clear cell renal carcinoma, basal cell carcinoma, lung cancer, breast/ovarian carcinoma, meningioma, neuroendocrine tumors, and some types of sarcomas were added to the syndrome spectrum.[89,114] However, the molecular mechanisms involved in these specific tumor types and in disease progression are not understood. Like other tumor suppressor genes, germline mutations in *BAP1* are inherited in an autosomal dominant manner. Although penetrance is incomplete and tumor may vary in different members of the same family, more than 80% of gene carriers are affected by at least one type of cancer.[115]

MPM is the second most common tumor identified in BAP1-TPDS, comprising 22% of tumors. Comparing with sporadic MPM, the median age of onset in germline-associated MPM is significantly earlier (74 and 46 years, respectively),[111] and survival rates are 7-fold longer.[116]

Despite the high relevance of germline mutations in *BAP1* in higher risk of developing hereditary MM and other tumors of the syndrome, a significant proportion of families with multiple mesothelioma cases do not have mutations in this gene, suggesting that other genes may predispose to these tumors.[117,118] Along this line, a recent study examined 94 hereditary cancer predisposition genes in 93 mesothelioma patients and detected likely pathogenic mutations in 10% of the cases, with an enrichment of mutations in genes of the homologous recombination DNA repair pathway. Interestingly, patients with mutations in these genes reported exposure to asbestos less frequently.[118]

Gene expression profile

Genetic alterations leading to phenotypic disorders produce altered gene expression profiles, knowledge of which may improve our understanding of relevant molecular pathways. Early studies using gene expression profiling in MM suggested the existence of two relevant molecular subtypes associated with histological classification: epithelioid and sarcomatoid.[119-121] Interestingly, genes associated with epithelioid-mesenchymal transition (EMT) were enriched in the sarcomatoid group, indicating a more mesenchymal phenotype.[121] Further work suggested that 4 subtypes can be distinguished and are associated with the spectrum from epithelioid to sarcomatoid histology, confirming the differential expression of EMT genes.[77,81] This was corroborated through data reanalysis, which showed that the molecular groups represent a continuum or histo-molecular gradient in which tumors can be dissected into a combination of epithelioid-like (E-score) and sarcomatoid-like (S-score) signatures, whose proportions are associated with prognosis.[122]

MPM TREATMENT

Prognostic factors

Established prognostic indicators, such as histologic subtype, age, and sex, can provide some information to predict patient survival, but there are few definitive and specific prognostic indicators routinely used to predict likely outcomes in individual patients. The European Organization for Research and Treatment of Cancer (EORTC) suggests that poor performance status, leukocytosis, sarcomatoid type, and male individuals are associated with poorer prognosis.[123] Meanwhile, the CALGB score includes age of 75 years, non-epithelioid histology, LDH 500UI/L, pleural involvement, platelets 400,000/mm3, chest pain, and poor PS as unfavorable prognostic factors.[124] Other prognostic indices include weight loss, hemoglobin, and serum albumin levels,[125] or WBC.[126]

In addition to its involvement in pathogenesis, systemic inflammation is associated with overall survival and response to treatment. Prognostic factors based on inflammatory response, which include the combination of C-reactive protein and albumin, the combination of neutrophil and lymphocyte counts (neutrophil-to-lymphocyte ratio, NLR), and the combination of platelet and lymphocyte counts are associated with survival in patients with various cancers, including MPM, with higher levels predicting poorer survival.[39]

Surgery

In the setting of resectable disease, treatment of MPM is based on trimodal therapy: surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy, especially in patients without lymph node involvement.[127]

Generally, prognosis is dismal, as most patients have unresectable disease at diagnosis or are considered inoperable due to age, performance status, or comorbidities. It is important for patients who are candidates for surgery to undergo EBUS (endobronchial ultrasound) or mediastinoscopy, as mediastinal lymph node dissemination is a poor prognostic factor in MPM.[14]

For resectable tumors, the three most commonly used surgical procedures in the treatment of mesothelioma are thoracoscopy with pleurodesis, pleurectomy/decortication, and extrapleural pneumonectomy.[43]

Pleurectomy/decortication is a surgical procedure aimed at reducing tumor burden. This procedure is performed through open thoracotomy and consists of removing the parietal pleura, including the portion adjacent to the mediastinum, pericardium, and diaphragm (often requiring removing a portion of the diaphragm), and removal of the visceral pleura to decorticate the lung. This treatment provides relief of local symptoms and prevents recurrence of pleural effusion, but usually implies a high rate of locoregional (80% to 90%) or distant recurrence (10% to 36%), in addition to being usually not curative.[43]

However, the role of pleurectomy/decortication is debatable. The MesoVATS trial compared talc pleurodesis with video-assisted thoracoscopic partial pleurectomy (VAT -PP). VAT-PP did not result in a better OS (HR =1.04; 95%CI 0.76-1.42; p=0.81) and had a higher rate of surgical complications (31% x 14%, p=0.019); in addition, quality of life at 6 months was better in the VAT -PP group.[128]

Extrapleural pneumonectomy (EPP) is considered a more aggressive technique for involving "*en bloc*" removal of tissue in the hemithorax, including visceral and parietal pleura, affected lung, mediastinal lymph nodes, diaphragm, and pericardium. It is not usually considered in patients with limiting comorbidities, low performance status, mediastinal lymph node involvement, or sarcomatoid histology because of the morbidity and mortality and poorer prognosis among these patients.[129]

Pleurodesis is a procedure to remove fluid accumulation in the pleural space. It involves drainage of the fluid through thoracoscopy under general anesthesia or sedation or by inserting a thoracic tube through thoracostomy. After removing the fluid, sclerosing chemicals are introduced into the pleural cavity to prevent the fluid from accumulating again.[130]

A comparison between extrapleural pneumonectomy or pleurectomy/decortication in 663 patients revealed significant differences in survival, with a 1.4-fold higher risk of death for extrapleural pneumonectomy (p=0.001), after controlling for disease stage, histology, gender, and multimodality therapy.[131] In another randomized controlled trial, patients receiving platinum-based neoadjuvant chemotherapy were randomized to extrapleural pneumonectomy or not. No survival or quality-of-life differences were observed between the groups.[132]

Radiotherapy

The main current indications for radiotherapy in MPM are: hemithoracic radiotherapy before or after extrapleural pneumonectomy, hemithoracic radiotherapy after decortication/pleurectomy, and palliative radiotherapy to relieve local symptoms.[133]

Radical hemithoracic radiotherapy (RHR) can be performed after extrapleural pneumonectomy to improve local control, although it is associated with in-field failure rates of 15% to 35%.[134] Although the topic is still debated, several treatment guidelines recommend RHR, such as the NCCN (National Comprehensive Cancer Center).

The SAKK 17/04 trial,[135] a prospective phase II, investigated the role of adjuvant RHR after platinum-based neoadjuvant chemotherapy followed by extrapleural pneumonectomy. Patients were randomized to radiotherapy vs observation. There was no significant difference between the groups. More recently, a phase III study compared RHR with palliative radiotherapy after non-radical lung sparing surgery and chemotherapy, reaching better OS in the RHR arm (2-year OS 58% x 28%; HR 0.58, 95CI 0.31-0.95, p=0.031), at the cost of higher grade 3/4 toxicity.[136]

The rationale for the use of neoadjuvant hemithoracic radiotherapy prior to extrapleural pneumonectomy arose from observing a frequent tumor spread to the contralateral lung and peritoneum, which may be related to surgery. The SMART (Surgery for Mesothelioma After Radiation Therapy) strategy[137] was developed to achieve lower spread rates associated with surgical intervention. The authors observed a median overall survival of 51 months and a median disease-free survival of 47 months for epithelioid pleural mesothelioma, suggesting such strategy to provide some benefit to this population.

Following the publication of controversial data from the MARS-1 study, the use of extrapleural pneumectomy has declined in recent years in favor of lung-sparing techniques, such as pleurectomy and lung decortication. The IMPRINT study, a prospective phase II trial, demonstrated the safety of delivering intensity-modulated radiotherapy to the hemithorax concurrently with chemotherapy in patients who had undergone pleurectomy and lung decortication.[138]

In the palliative context, radiotherapy can be used to control a range of symptoms for which drug treatment is sometimes inadequate, such as chest pain associated with chest wall invasion, hemoptysis, cough or dyspnea, as well as to prevent spinal cord compression.[139]

Systemic treatment

Systemic chemotherapy is the treatment of choice in the setting of unresectable disease and for patients with relapsed disease or that do not wish to have surgery[9] (Figure 4). In first-line chemotherapy, regimens containing platinum have higher response rates than platinum-free regimens.[140] Pemetrexed-based regimens have been the first-line systemic chemotherapy option in most institutions, although no consensus has been reached on which agent(s) should be used to supplement pemetrexed.[9] Substituting cisplatin with carboplatin resulted in an ORR of 25-29%, but with better toxicity profile and similar OS.[141]

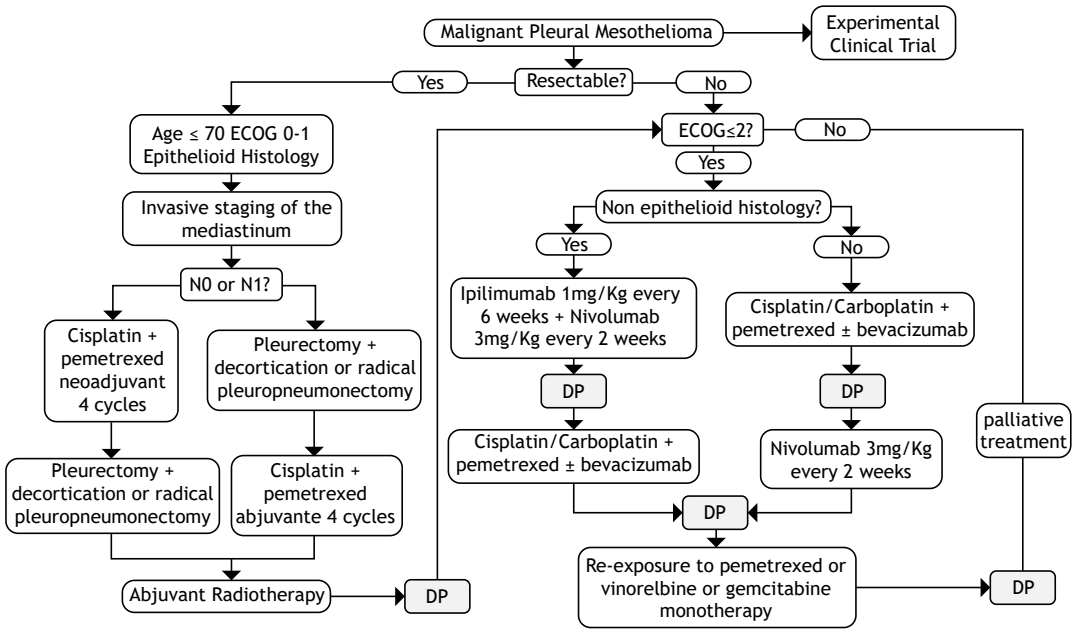

Figure 4. Diagram summarizing current treatment for MPM. It should be highlighted that, if available, all patients must be considered for participation in investigational clinical trials.
DP: disease progression.

The addition of bevacizumab to cisplatin and pemetrexed in the first-line setting improved OS (18.8 months vs. 16.1 months) and progression-free survival (PFS) (9.2 months vs. 7.3 months) compared with cisplatin and pemetrexed in a recent phase III study (MAPS).[142] However, the use of anti-angiogenic drugs in combination with chemotherapy is not widespread, as other trials testing angiokinase inhibitors, such as cediranib and nintedanib, were negative.[5,143,144] Nevertheless, ramucirumab, an anti-VEGFR-2 antibody, was combined with gemcitabine in a randomized phase II trial (RAMES trial) and compared with gemcitabine as a single agent in second-line MPM not previously treated with antiangiogenic drugs. The combination doubled median OS (7.5 x 13.8 months) and median PFS (3.3 x 6.2 months), although no difference in ORR was observed.[145]

The use of immune checkpoint inhibitors (ICI) has revolutionized the treatment of various tumor types in recent years.[26] Immunotherapy is a treatment modality that explores the patient's immune system to eliminate tumor cells. Examples of immunotherapeutic approaches currently under investigation include inhibitors of T-cell immune checkpoints or agonists of T-cell activation pathways, the use of cytokines such as IL-12 and IL-15, therapeutic vaccines, elimination of immunosuppressive cells, and modulation of other components of the immune response.[146]

CTLA4 is a T cell receptor that plays a key role in preventing T cell hyperactivation.[147] CTLA4 signaling decreases T cell activation and the ability of memory T cells to support an immune response.[148] Greater inhibition of tumor growth was observed upon administering anti-CTLA4 monoclonal antibody between cycles of cisplatin in mesothelioma mouse models.[149] Furthermore, CTLA4 blockade alternating with cisplatin treatment inhibited tumor cell proliferation while increasing the number of T lymphocytes infiltrating the tumor. Despite these results, DETERMINE, a multicenter, randomized, placebo-controlled phase IIB trial, failed to show any improvement in OS with the use of tremelimumab (an anti-CTLA4 antibody) in relation to placebo in second- and third-line[150] (Table 3).

PD1 is also an immune checkpoint and has two ligands: PD -L1 and PD -L2. Overexpression of the PD1 receptor plays a key role in T cell exhaustion and is an important factor during the normal immune response in preventing the onset of autoimmunity.[158] PD-L1 is highly expressed in MPM.[159] Positive PD-L1 expression was reported in 40% of 106 mesothelioma specimens, 21% in the epithelioid subtype, 94% in the sarcomatoid subtype, and 57% in the biphasic subtype.[160] Some studies reported worse survival rates in cases of MM with tumor PD-L1 expression,[161,162] whereas others reported no significant difference in survival between cases of MM with and without PD-L1 expression.[163]

Several phase II trials investigated the activity of anti-PD1 antibodies as second-line therapy for pleural mesothelioma and reported an ORR of 9.4-29% and a median PFS of 2.6-6.2 months. Recently, however, a phase III trial (PROMISE-meso) randomized 144 patients with advanced MM who had progressed to previous systemic chemotherapy to receive pembrolizumab or chemotherapy (gemcitabine or vinorelbine). There was no significant difference in PFS (primary endpoint) or OS, but response rate was higher among

Table 3. Trials evaluating immunotherapy in second line for MPM.

Trial	Phase	Arms	N	ORR (%)	PFS median (months)	OS median (months)	PD-L1 Expression
DETERMINE	II	Tremelimumab	569	5	2.8	7.7	NE
KEYNOTE-028[151]	IB	Pembrolizumab	25	20	5.4	18	All tumors were PD-L1+
Kindler et al.[152]	II	Pembrolizumab	35	21	6.2	NR	NA
NivoMes[153]	II	Nivolumab	34	24	2.6	11.8	Trend to higher ORR
MERIT[154]	II	Nivolumab	34	29	6.1	17.3	Improved PFS and OS
JAVELIN[155]	IB	Avelumab	53	9.4	4.3	NR	Trend to improved PFS
NIBIT-MESO-1[156]	II	Tremelimumab + durvalumab	40	25	5.7	16.6	Improved ORR, OS and PFS
INITIATE[157]	II	Nivolumab + ipilimumab	36	29	6.2	NR	Improved ORR
MAPS2	II (randomized)	Nivolumab + ipilimumab Nivolumab	125	28 9	5.6 4.0	15.9 11.9	No association with OS or PFS
PROMISE	III	Pembrolizumab Gemcitabine or Vinorelbine	144	20	2.5 3.4	10.7 12.4	NA
CONFIRM	III	Nivolumab BSC	332	NR	4.2 2.8	9.1 9.7	NA

NE: not evaluated; NA: no association; NR: not reported; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; BSC: best supportive care, N: number of subjects.

patients treated with pembrolizumab (22% x 6%). No association with PD-L1 expression was observed.[164] In contrast, the CONFIRM trial compared nivolumab with placebo in the same scenario and found improved OS (9.2 vs 6.6 months; HR 0.72; 95%CI 0.55-0.94; p=0.02) and PFS (3.0 vs 1.8 months; HR 0.62; 95%CI 0.49-0.78; p 0.001).[165] This suggests that ICIs are active against MM, although not superior to chemotherapy when used in second or further lines.

A French multicenter, randomized, phase II study (MAPS-2) compared nivolumab (anti-PD1) with nivolumab in combination with ipilimumab (anti-CTLA4) in patients who had failed first- or second-line therapy. The 12-week disease control rate was 44% in the nivolumab group and 50% in the combination group. High expression of PD-L1 was associated with a higher response rate.[5] Other phase II studies showed similar results (Table 3).

In the wake of these promising results, the CheckMate-743 trial, a randomized phase III trial, compared the combination of ipilimumab and nivolumab (IO+IO) with cisplatin/carboplatin plus pemetrexed as first-line therapy for unresectable MPM. The study showed a longer OS in the group of patients treated with IO+IO (18.1 x 14.1 months; HR 0.74 95%CI 0.6-0.91; p=0.002). OS at 2 years was 41% and 27% for IO+IO and chemotherapy, respectively. Both histologies benefited from treatment with IO+IO, although the relative improvement was greater in patients with non-epithelioid tumors. CheckMate-743 established this combination as the new standard first-line therapy for metastatic or unresectable MPM.

There is no consensus regarding second-line systemic therapy for advanced pleural mesothelioma, and commonly used drugs are associated with poor response rates and short median survival.[166] Patients who benefited from previous treatment with pemetrexed-containing regimens or who have not been previously exposed to pemetrexed may be treated with pemetrexed,[167,168] otherwise, patients are treated with gemcitabine, vinorelbine, or doxorubicin.[169] Vinorelbine is the only drug directly compared with best supportive care as second-line therapy in advanced MM in a randomized trial (VIM trial) and was associated with improved PFS (median PFS: 4.2 x 2.8 months; HR 0.59; 95%CI 0.41-0.85; one-sided p=0.0017), but had no impact on OS.[165] Figure 4 summarizes the current management of pleural mesothelioma.

More recently, two single-arm phase 2 trials investigated the role of durvalumab in combination with standard platinum- and pemetrexed-based chemotherapy in the first-line treatment of MPM. The first study (PrECOG 0505) showed a median OS of 20.4 months.[170] The OS was 70.4% at 12 months and 44.2% at 24 months. The second study (DREAM) showed a median OS of 18.4 months, a median PFS of 6.7 months, and an ORR of 48%.[171] Given the promising results, a phase III trial will start enrollment soon.

There are several ongoing clinical trials investigating new therapies for MPM (Table 4), and the future is likely to bring new hope for these patients.

Table 4. Ongoing phase III first line treatment trials for Malignant Pleural Mesothelioma.

TITLE	PRIMARY ID	CLINICALTRIALS ID
PHASE III RANDOMIZED TRIAL OF PLEURECTOMY/ DECORTICATION PLUS CHEMOTHERAPY WITH OR WITHOUT ADJUVANT HEMITHORACIC INTENSITY-MODULATED PLEURAL RADIATION THERAPY (IMPRINT) FOR MPM.	NRG-LU006	NCT04158141
RANDOMIZED, DOUBLE-BLIND, PHASE 2/3 STUDY IN SUBJECTS WITH MPM TO ASSESS ADI-PEG 20 WITH PEMETREXED AND CISPLATIN (ATOMIC-MESO PHASE 2/3 STUDY).	POLARIS2015-003	NCT02709512
A PHASE III, RANDOMIZED, OPEN LABEL TRIAL OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB VERSUS PEMETREXED WITH CISPLATIN OR CARBOPLATIN AS FIRST LINE THERAPY IN UNRESECTABLE MPM	CA209-743	NCT02899299
A MULTICENTRE RANDOMISED PHASE III TRIAL COMPARING ATEZOLIZUMAB PLUS BEVACIZUMAB AND STANDARD CHEMOTHERAPY VERSUS BEVACIZUMAB AND STANDARD CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR ADVANCED MPM.	ETOP 13-18	NCT03762018
A RANDOMIZED, OPEN-LABEL PHASE II/III STUDY WITH DENDRITIC CELLS LOADED WITH ALLOGENEIC TUMOUR CELL LYSATE (PHERALYS) IN SUBJECTS WITH MESOTHELIOMA AS MAINTENANCE TREATMENT (MESOPHER) AFTER CHEMOTHERAPY.	MM04	NCT03610360
A PHASE II/III RANDOMIZED STUDY OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MPM.	IFCT-1901	NCT02784171

CONCLUSION

MPM is largely preventable and global efforts should be made to ban the asbestos industry once and for all. Despite some recent advances, this rare but serious condition still represents an unmet medical need and lacks robust prospective studies to better understand its pathophysiology, as well as randomized trials to define more effective treatments for patients.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Translational Oncology and Innovation (INCITO-INOTE). CAPES fellowships to CHC and GV are gratefully acknowledged.

AUTHOR CONTRIBUTIONS

GNMH: final manuscript review and submission, manuscript draft elaboration, literature review, table and graphics construction, conceptualization.

CHC: manuscript draft elaboration, literature review.

CALP: manuscript draft elaboration, literature review, pathological specimens microphotographies.

GV: manuscript draft elaboration, literature review.

JRN: manuscript draft elaboration, literature review.

VCCL: final manuscript review, manuscript draft elaboration, literature review, table and graphics construction, treatment flow chart elaboration, conceptualization, oversight.

REFERENCES

1. Marinaccio A, Binazzi A, Marzio DD, Scarselli A, Verardo M, Mirabelli D, et al. Pleural malignant mesothelioma epidemic: Incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. Int J Cancer. 2012;130(9):2146-54. http://dx.doi.org/10.1002/ijc.26229. PMid:21647880.
2. Grondin SC, Sugarbaker DJ. Malignant mesothelioma of the pleural space. Oncology. 1999;13(7):919-26. PMid:10442339.
3. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Les décés mondiaux par mésothéliome rapportés á l'Organisation mondiale de la Santé entre 1994 et 2008. Bull World Health Organ. 2011;89(10):716-24. http://dx.doi.org/10.2471/BLT.11.086678. PMid:22084509.
4. Bridda A, Padoan I, Mencarelli R, Frego M. Peritoneal mesothelioma: a review. MedGenMed. 2007;9(2):32. PMid:17955087.
5. Scherpereel A, Wallyn F, Albelda SM, Munck C. Novel therapies for malignant pleural mesothelioma. Lancet Oncol. 2018;19(3):e161-72. http://dx.doi.org/10.1016/S1470-2045(18)30100-1. PMid:29508763.
6. Henley SJ, Larson TC, Wu M, Antao VC, Lewis M, Pinheiro GA, et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003- 2008. Int J Occup Environ Health. 2013;19(1):1-10. http://dx.doi.org/10.1179/2049396712Y.0000000016. PMid:23582609.
7. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant pleural mesothelioma. J Clin Oncol. 2009;27(12):2081-90. http://dx.doi.org/10.1200/JCO.2008.19.8523. PMid:19255316.

8. Ai J, Stevenson JP. Current issues in malignant pleural mesothelioma evaluation and management. Oncologist. 2014;19(9):975-84. http://dx.doi.org/10.1634/theoncologist.2014-0122. PMid:25061089.
9. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. Ann Transl Med. 2017;5(11):236. http://dx.doi.org/10.21037/atm.2017.03.96. PMid:28706904.
10. Price B, Ware A. Special Article. J Am Med Assoc. 1946;131(13):1053. http://dx.doi.org/10.1001/jama.1946.02870300021006.
11. Algranti E, Saito CA, Carneiro APS, Moreira B, Mendonça EMC, Bussacos MA. The next mesothelioma wave: mortality trends and forecast to 2030 in Brazil. Cancer Epidemiol. 2015;39(5):687-92. http://dx.doi.org/10.1016/j.canep.2015.08.007. PMid:26320384.
12. Pedra F, Tambellini AT, Pereira BB, da Costa ACC, Castro HA. Mesothelioma mortality in Brazil, 1980-2003. Int J Occup Environ Health. 2008;14(3):170-5. http://dx.doi.org/10.1179/oeh.2008.14.3.170. PMid:18686716.
13. Pedra F, Silva PO, Mattos IA, Castro H. Mortalidade por mesotelioma no Brasil, 1980 a 2010. Rev Bras Cancerol. 2014;60(3):199-206. http://dx.doi.org/10.32635/2176-9745.RBC.2014v60n3.464.
14. Carbone M, Adusumilli PS, Alexander HR Jr, Baas P, Bardelli F, Bononi A, et al. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. CA Cancer J Clin. 2019;69(5):402-29. http://dx.doi.org/10.3322/caac.21572. PMid:31283845.
15. Panou V, Gadiraju M, Wolin A, Weipert CM, Skarda E, Husain AN, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. J Clin Oncol. 2018;36(28):2863-71. http://dx.doi.org/10.1200/JCO.2018.78.5204. PMid:30113886.
16. Pastorino S, Yoshikawa Y, Pass HI, Emi M, Nasu M, Pagano I, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. J Clin Oncol. 2018;36(35):3485-94. http://dx.doi.org/10.1200/JCO.2018.79.0352. PMid:30376426.
17. Yang H, Testa JR, Carbone M. Mesothelioma epidemiology, carcinogenesis, and pathogenesis. Curr Treat Options Oncol. 2008;9(2-3):147-57. http://dx.doi.org/10.1007/s11864-008-0067-z. PMid:18709470.
18. Capelozzi VL. Asbesto, asbestose e câncer: critérios diagnósticos. J Pneumol. 2001;27(4):206-18. http://dx.doi.org/10.1590/S0102-35862001000400007.
19. Carbone M, Kratzke RA, Testa JR. The pathogenesis of mesothelioma. Semin Oncol. 2002;29(1):2-17. http://dx.doi.org/10.1053/sonc.2002.30227. PMid:11836664.
20. Zucali PA, Ceresoli GL, De Vincenzo F, Simonelli M, Lorenzi E, Gianoncelli L, et al. Advances in the biology of malignant pleural mesothelioma. Cancer Treat Rev. 2011;37(7):543-58. http://dx.doi.org/10.1016/j.ctrv.2011.01.001. PMid:21288646.
21. Driscoll KE, Maurer JK, Higgins J, Poynter J. Alveolar macrophage cytokine and growth factor production in a rat model of crocidolite-induced pulmonary inflammation and fibrosis. J Toxicol Environ Health. 1995;46(2):155-69. http://dx.doi.org/10.1080/15287399509532026. PMid:7563215.
22. Marchi E, Liu W, Broaddus VC. Mesothelial cell apoptosis is confirmed in vivo by morphological change in cytokeratin distribution. Am J Physiol Lung Cell Mol Physiol. 2000;278(3):L528-35. http://dx.doi.org/10.1152/ajplung.2000.278.3.L528. PMid:10710525.
23. Leard LE, Broaddus VC. Mesothelial cell proliferation and apoptosis. Respirology. 2004;9(3):292-9. http://dx.doi.org/10.1111/j.1440-1843.2004.00602.x. PMid:15362999.
24. Cugell DW, Kamp DW. Asbestos and the pleura: a review. Chest. 2004;125(3):1103-17. http://dx.doi.org/10.1378/chest.125.3.1103. PMid:15006974.
25. Mutsaers SE. Mesothelial cells: their structure, function and role in serosal repair. Respirology. 2002;7(3):171-91. http://dx.doi.org/10.1046/j.1440-1843.2002.00404.x. PMid:12153683.
26. Suzuki K, Kadota K, Sima CS, Sadelain M, Rusch VW, Travis WD, et al. Chronic inflammation in tumor stroma is an independent predictor of prolonged survival in epithelioid malignant pleural mesothelioma patients. Cancer Immunol Immunother. 2011;60(12):1721-8. http://dx.doi.org/10.1007/s00262-011-1073-8. PMid:21769693.
27. Ramos-Nino ME, Testa JR, Altomare DA, Pass HI, Carbone M, Bocchetta M, et al. Cellular and molecular parameters of mesothelioma. J Cell Biochem. 2006;98(4):723-34. http://dx.doi.org/10.1002/jcb.20828. PMid:16795078.
28. Lukacs NW, Hogaboam C, Chensue SW, Blease K, Kunkel SL. Type 1/type 2 cytokine paradigm and the progression of pulmonary fibrosis. Chest. 2001;120(1, Supl.):5S-8S. http://dx.doi.org/10.1378/chest.120.1_suppl.S5. PMid:11451879.
29. Manning CB, Cummins AB, Jung MW, Berlanger I, Timblin CR, Palmer C, et al. A mutant epidermal growth factor receptor targeted to lung epithelium inhibits asbestos-induced proliferation and proto-oncogene expression. Cancer Res. 2002;62(15):4169-75. PMid:12154012.
30. Pfau JC, Li S, Holland S, Sentissi JJ. Alteration of fibroblast phenotype by asbestos-induced autoantibodies. J Immunotoxicol. 2011;8(2):159-69. http://dx.doi.org/10.3109/1547691X.2011.562257. PMid:21457077.
31. Yang H, Bocchetta M, Kroczynska B, Elmishad AG, Chen Y, Liu Z, et al. TNF-α inhibits asbestos-induced cytotoxicity via a NF-κB-dependent pathway, a possible mechanism for asbestos-induced oncogenesis. Proc Natl Acad Sci USA. 2006;103(27):10397-402. http://dx.doi.org/10.1073/pnas.0604008103. PMid:16798876.
32. Huang SXL, Jaurand M-C, Kamp DW, Whysner J, Hei TK. Role of mutagenicity in asbestos fiber-induced carcinogenicity and other diseases. J Toxicol Environ Health B Crit Rev. 2011;14(1-4):179-245. http://dx.doi.org/10.1080/10937404.2011.556051. PMid:21534089.
33. Mossman BT, Lippmann M, Hesterberg TW, Kelsey KT, Barchowsky A, Bonner JC. Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health B Crit Rev. 2011;14(1-4):76-121. http://dx.doi.org/10.1080/10937404.2011.556047. PMid:21534086.
34. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440(7081):237-41. http://dx.doi.org/10.1038/nature04516. PMid:16407889.
35. Dostert C, Pétrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science. 2008;320(5876):674-7. http://dx.doi.org/10.1126/science.1156995. PMid:18403674.
36. Cornelissen R, Lievense LA, Maat AP, Hendriks RW, Hoogsteden HC, Bogers AJ, et al. Ratio of intratumoral macrophage phenotypes is a prognostic factor in epithelioid malignant pleural mesothelioma. PLoS One. 2014;9(9):e106742. http://dx.doi.org/10.1371/journal.pone.0106742. PMid:25192022.
37. Ujiie H, Kadota K, Nitadori J-I, Aerts JG, Woo KM, Sima CS, et al. The tumoral and stromal immune microenvironment in malignant pleural mesothelioma: a comprehensive analysis reveals prognostic immune markers. OncoImmunology. 2015;4(6):e1009285. http://dx.doi.org/10.1080/2162402X.2015.1009285. PMid:26155428.
38. Linton A, van Zandwijk N, Reid G, Clarke S, Cao C, Kao S. Inflammation in malignant mesothelioma - friend or foe? Ann Cardiothorac Surg. 2012;1(4):516-22. PMid:23977546.
39. Yamagishi T, Fujimoto N, Nishi H, Miyamoto Y, Hara N, Asano M, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with malignant pleural mesothelioma. Lung Cancer. 2015;90(1):111-7. http://dx.doi.org/10.1016/j.lungcan.2015.07.014. PMid:26259877.
40. Pass HI, Carbone M. Current status of screening for malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg. 2009;21(2):97-104. http://dx.doi.org/10.1053/j.semtcvs.2009.06.007. PMid:19822280.
41. Enewold L, Sharon E, Thomas A. Patterns of care and survival among patients with malignant mesothelioma in the United States. Lung Cancer. 2017;112:102-8. http://dx.doi.org/10.1016/j.lungcan.2017.08.009. PMid:29191582.
42. Nelson DB, Rice DC, Niu J, Atay S, Vaporciyan AA, Antonoff M, et al. Long-term survival outcomes of cancer-directed surgery for malignant pleural mesothelioma: propensity score matching analysis. J Clin Oncol. 2017;35(29):3354-62. http://dx.doi.org/10.1200/JCO.2017.73.8401. PMid:28817374.
43. Ismail-Khan R, Robinson LA, Williams CC Jr, Garrett CR, Bepler G, Simon GR. Malignant pleural mesothelioma: a comprehensive review. Cancer Control. 2006;13(4):255-63. http://dx.doi.org/10.1177/107327480601300402. PMid:17075562.
44. Otsuka H, Terazawa K, Morita N, Otomi Y, Yamashita K, Nishitani H. Is FDG-PET/CT useful for managing malignant pleural mesothelioma? J Med Invest. 2009;56(1-2):16-20. http://dx.doi.org/10.2152/jmi.56.16. PMid:19262009.
45. Galateau Salle F, Le Stang N, Nicholson AG, Pissaloux D, Churg A, Klebe S, et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the International Mesothelioma Panel From the MESOPATH Reference Center. J Thorac Oncol. 2018;13(8):1189-203. http://dx.doi.org/10.1016/j.jtho.2018.04.023. PMid:29723687.
46. Husain AN, Colby TV, Ordóñez NG, Allen TC, Attanoos RL, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2018;142(1):89-108. http://dx.doi.org/10.5858/arpa.2017-0124-RA. PMid:28686500.

47. Kadota K, Suzuki K, Colovos C, Sima CS, Rusch VW, Travis WD, et al. A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma. Mod Pathol. 2012;25(2):260-71. http://dx.doi.org/10.1038/modpathol.2011.146. PMid:21983936.
48. Rosen LE, Karrison T, Ananthanarayanan V, Gallan AJ, Adusumilli PS, Alchami FS, et al. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. Mod Pathol. 2018;31(4):598-606. http://dx.doi.org/10.1038/modpathol.2017.170. PMid:29327706.
49. Meyerhoff RR, Yang C-FJ, Speicher PJ, Gulack BC, Hartwig MG, D'Amico TA, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res. 2015;196(1):23-32. http://dx.doi.org/10.1016/j.jss.2015.01.043. PMid:25791825.
50. Beasley MB, Galateau-Salle F, Dacic S. Pleural mesothelioma classification update. Virchows Arch. 2021;478(1):59-72. http://dx.doi.org/10.1007/s00428-021-03031-7. PMid:33475835.
51. Boutin C, Rey F. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 1: diagnosis. Cancer. 1993;72(2):389-93. http://dx.doi.org/10.1002/1097-0142(19930715)72:2<389::AID-CNCR2820720213>3.0.CO;2-V. PMid:8319170.
52. Nicholson AG, Sauter JL, Nowak AK, Kindler HL, Gill RR, Remy-Jardin M, et al. EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach. J Thorac Oncol. 2020;15(1):29-49. http://dx.doi.org/10.1016/j.jtho.2019.08.2506. PMid:31546041.
53. Churg A, Naso JR. The separation of benign and malignant mesothelial proliferations. Am J Surg Pathol. 2020;44(11):e100-12. http://dx.doi.org/10.1097/PAS.0000000000001565. PMid:32826526.
54. Henderson DW, Reid G, Kao SC, Van Zandwijk N, Klebe S. Challenges and controversies in the diagnosis of mesothelioma: Part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol. 2013;66(10):847-53. http://dx.doi.org/10.1136/jclinpath-2012-201303. PMid:23814259.
55. Karpathiou G, Hiroshima K, Peoc'h M. Adenomatoid tumor: a review of pathology with focus on unusual presentations and sites, histogenesis, differential diagnosis, and molecular and clinical aspects with a historic overview of its description. Adv Anat Pathol. 2020;27(6):394-407. http://dx.doi.org/10.1097/PAP.0000000000000278. PMid:32769378.
56. Hung YP, Chirieac LR. Pathology of malignant pleural mesothelioma. Thorac Surg Clin. 2020;30(4):367-82. http://dx.doi.org/10.1016/j.thorsurg.2020.08.007. PMid:33012427.
57. Cheng JQ, Jhanwar SC, Klein WM, Bell DW, Lee WC, Altomare DA, et al. p16 alterations and deletion mapping of 9p21-p22 in malignant mesothelioma. Cancer Res. 1994;54(21):5547-51. PMid:7923195.
58. Xio S, Li D, Vijg J, Sugarbaker DJ, Corson JM, Fletcher JA. Codeletion of p15 and p16 in primary malignant mesothelioma. Oncogene. 1995;11(3):511-5. PMid:7630635.
59. Sekido Y, Pass HI, Bader S, Mew DJ, Christman MF, Gazdar AF, et al. Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but not in lung cancer. Cancer Res. 1995;55(6):1227-31. PMid:7882313.
60. Bianchi AB, Mitsunaga SI, Cheng JQ, Klein WM, Jhanwar SC, Seizinger B, et al. High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesotheliomas. Proc Natl Acad Sci USA. 1995;92(24):10854-8. http://dx.doi.org/10.1073/pnas.92.24.10854. PMid:7479897.
61. Björkqvist A-M, Wolf M, Nordling S, Tammilehto L, Knuuttila A, Kere J, et al. Deletions at 14q in malignant mesothelioma detected by microsatellite marker analysis. Br J Cancer. 1999;81(7):1111-5. PMid:10584869.
62. Prins JB, Williamson KA, Kamp MM, Van Hezik EJ, Van der Kwast TH, Hagemeijer A, et al. The gene for the cyclin-dependent-kinase-4 inhibitor, CDKN2A, is preferentially deleted in malignant mesothelioma. Int J Cancer. 1997;95(4):649-53. PMid:9466670.
63. Taniguchi T, Karnan S, Fukui T, Yokoyama T, Tagawa H, Yokoi K, et al. Genomic profiling of malignant pleural mesothelioma with array-based comparative genomic hybridization shows frequent non-random chromosomal alteration regions including JUN amplification on 1p32. Cancer Sci. 2007;98(3):438-46. http://dx.doi.org/10.1111/j.1349-7006.2006.00386.x. PMid:17270034.
64. Ivanov SV, Miller J, Lucito R, Tang C, Ivanova AV, Pei J, et al. Genomic events associated with progression of pleural malignant mesothelioma. Int J Cancer. 2009;124(3):589-99. http://dx.doi.org/10.1002/ijc.23949. PMid:18973227.
65. Cheung M, Pei J, Pei Y, Jhanwar SC, Pass HI, Testa JR. The promyelocytic leukemia zinc-finger gene, PLZF, is frequently downregulated in malignant mesothelioma cells and contributes to cell survival. Oncogene. 2010;29(11):1633-40. http://dx.doi.org/10.1038/onc.2009.455. PMid:20010871.
66. Takeda M, Kasai T, Enomoto Y, Takano M, Morita K, Kadota E, et al. Genomic gains and losses in malignant mesothelioma demonstrated by FISH analysis of paraffin-embedded tissues. J Clin Pathol. 2012;65(1):77-82. http://dx.doi.org/10.1136/jclinpath-2011-200208. PMid:22081786.
67. Bott M, Brevet M, Taylor BS, Shimizu S, Ito T, Wang L, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. Nat Genet. 2011;43(7):668-72. http://dx.doi.org/10.1038/ng.855. PMid:21642991.
68. Yoshikawa Y, Sato A, Tsujimura T, Emi M, Morinaga T, Fukuoka K, et al. Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma. Cancer Sci. 2012;103(5):868-74. http://dx.doi.org/10.1111/j.1349-7006.2012.02223.x. PMid:22321046.
69. Guo G, Chmielecki J, Goparaju C, Heguy A, Dolgalev I, Carbone M, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. Cancer Res. 2015;75(2):264-9. http://dx.doi.org/10.1158/0008-5472.CAN-14-1008. PMid:25488749.
70. Lo Iacono M, Monica V, Righi L, Grosso F, Libener R, Vatrano S, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. J Thorac Oncol. 2015;10(3):492-9. http://dx.doi.org/10.1097/JTO.0000000000000436. PMid:25514803.
71. Nasu M, Emi M, Pastorino S, Tanji M, Powers A, Luk H, et al. High incidence of somatic BAP1 alterations in sporadic malignant mesothelioma. J Thorac Oncol. 2015;10(4):565-76. http://dx.doi.org/10.1097/JTO.0000000000000471. PMid:25658628.
72. Borczuk AC, Pei J, Taub RN, Levy B, Nahum O, Chen J, et al. Genome-wide analysis of abdominal and pleural malignant mesothelioma with DNA arrays reveals both common and distinct regions of copy number alteration. Cancer Biol Ther. 2016;17(3):328-35. http://dx.doi.org/10.1080/15384047.2016.1145850. PMid:26853494.
73. Kato S, Tomson BN, Buys TPH, Elkin SK, Carter JL, Kurzrock R. Genomic landscape of malignant mesotheliomas. Mol Cancer Ther. 2016;15(10):2498-507. http://dx.doi.org/10.1158/1535-7163.MCT-16-0229. PMid:27507853.
74. Kang HC, Kim HK, Lee S, Mendez P, Kim W, Woodard G, et al. Whole exome and targeted deep sequencing identify genome- wide allelic loss and frequent SETDB1 mutations in malignant pleural mesotheliomas. Oncotarget. 2016;7(7):8321-31. http://dx.doi.org/10.18632/oncotarget.7032. PMid:26824986.
75. Ugurluer G, Chang K, Gamez ME, Arnett AL, Jayakrishnan R, Miller RC, et al. Genome-based mutational analysis by next generation sequencing in patients with malignant pleural and peritoneal mesothelioma. Anticancer Res. 2016;36(5):2331-8. PMid:27127140.
76. Chirac P, Maillet D, Leprêtre F, Isaac S, Glehen O, Figeac M, et al. Genomic copy number alterations in 33 malignant peritoneal mesothelioma analyzed by comparative genomic hybridization array. Hum Pathol. 2016;55:72-82. http://dx.doi.org/10.1016/j.humpath.2016.04.015. PMid:27184482.
77. Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet. 2016;48(4):407-16. http://dx.doi.org/10.1038/ng.3520. PMid:26928227.
78. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, Ohmuraya M, Sato A, Tsujimura T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. Proc Natl Acad Sci USA. 2016;113(47):13432-7. http://dx.doi.org/10.1073/pnas.1612074113. PMid:27834213.
79. Desmeules P, Joubert P, Zhang L, Al-Ahmadie HA, Fletcher CD, Vakiani E, et al. A subset of malignant mesotheliomas in young adults are associated with recurrent EWSR1/FUS-ATF1 fusions. Am J Surg Pathol. 2017;41(7):980-8. http://dx.doi.org/10.1097/PAS.0000000000000864. PMid:28505004.
80. Hung YP, Dong F, Watkins JC, Nardi V, Bueno R, Dal Cin P, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. JAMA Oncol. 2018;4(2):235-8. http://dx.doi.org/10.1001/jamaoncol.2017.2918. PMid:28910456.
81. Hmeljak J, Sanchez-Vega F, Hoadley KA, Shih J, Stewart C, Heiman D, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov. 2018;8(12):1548-65. http://dx.doi.org/10.1158/2159-8290.CD-18-0804. PMid:30322867.

82. Hassan R, Morrow B, Thomas A, Walsh T, Lee MK, Gulsuner S, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. Proc Natl Acad Sci USA. 2019;116(18):9008-13. http://dx.doi.org/10.1073/pnas.1821510116. PMid:30975761.
83. Nastase A, Mandal A, Lu SK, Anbunathan H, Morris-Rosendahl D, Zhang YZ, et al. Multiple therapeutic pathways in malignant mesothelioma identified by genomic mapping. medRxiv. 2020. In press.
84. Quetel L, Meiller C, Assié JB, Blum Y, Imbeaud S, Montagne F, et al. Genetic alterations of malignant pleural mesothelioma: association with tumor heterogeneity and overall survival. Mol Oncol. 2020;14(6):1207-23. http://dx.doi.org/10.1002/1878-0261.12651. PMid:32083805.
85. Cheng JQ, Lee WC, Klein MA, Cheng GZ, Jhanwar SC, Testa JR. Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: evidence for a two-hit mechanism of NF2 inactivation. Genes Chromosomes Cancer. 1999;24(3):238-42. http://dx.doi.org/10.1002/(SICI)1098-2264(199903)24:3<238::AID-GCC9>3.0.CO;2-M. PMid:10451704.
86. De Rienzo A, Archer MA, Yeap BY, Dao N, Sciaranghella D, Sideris AC, et al. Gender-specific molecular and clinical features underlie malignant pleural mesothelioma. Cancer Res. 2016;76(2):319-28. http://dx.doi.org/10.1158/0008-5472.CAN-15-0751. PMid:26554828.
87. Lindholm PM, Salmenkivi K, Vauhkonen H, Nicholson AG, Anttila S, Kinnula VL, et al. Gene copy number analysis in malignant pleural mesothelioma using oligonucleotide array CGH. Cytogenet Genome Res. 2007;119(1-2):46-52. http://dx.doi.org/10.1159/000109618. PMid:18160781.
88. Murthy SS, Testa JR. Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. J Cell Physiol. 1999;180(2):150-7. http://dx.doi.org/10.1002/(SICI)1097-4652(199908)180:2<150::AID-JCP2>3.0.CO;2-H. PMid:10395284.
89. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43(10):1022-5. http://dx.doi.org/10.1038/ng.912. PMid:21874000.
90. Jennings CJ, Murer B, O'Grady A, Hearn LM, Harvey BJ, Kay EW, et al. Differential p16/INK4A cyclin-dependent kinase inhibitor expression correlates with chemotherapy efficacy in a cohort of 88 malignant pleural mesothelioma patients. Br J Cancer. 2015;113(1):69-75. http://dx.doi.org/10.1038/bjc.2015.187. PMid:26057448.
91. López-Ríos F, Chuai S, Flores R, Shimizu S, Ohno T, Wakahara K, et al. Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. Cancer Res. 2006;66(6):2970-9. http://dx.doi.org/10.1158/0008-5472.CAN-05-3907. PMid:16540645.
92. Dacic S, Kothmaier H, Land S, Shuai Y, Halbwedl I, Morbini P, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. Virchows Arch. 2008;453(6):627-35. http://dx.doi.org/10.1007/s00428-008-0689-3. PMid:18958493.
93. Li W, You L, Cooper J, Schiavon G, Pepe-Caprio A, Zhou L, et al. Merlin/NF2 suppresses tumorigenesis by inhibiting the E3 ubiquitin ligase CRL4(DCAF1) in the nucleus. Cell. 2010;140(4):477-90. http://dx.doi.org/10.1016/j.cell.2010.01.029. PMid:20178741.
94. Mizuno T, Murakami H, Fujii M, Ishiguro F, Tanaka I, Kondo Y, et al. YAP induces malignant mesothelioma cell proliferation by upregulating transcription of cell cycle-promoting genes. Oncogene. 2012;31(49):5117-22. http://dx.doi.org/10.1038/onc.2012.5. PMid:22286761.
95. Urso L, Calabrese F, Favaretto A, Conte P, Pasello G. Critical review about MDM2 in cancer: possible role in malignant mesothelioma and implications for treatment. Crit Rev Oncol Hematol. 2016;97:220-30. http://dx.doi.org/10.1016/j.critrevonc.2015.08.019. PMid:26358421.
96. Walter RFH, Mairinger FD, Ting S, Vollbrecht C, Mairinger T, Theegarten D, et al. MDM2 is an important prognostic and predictive factor for platin-pemetrexed therapy in malignant pleural mesotheliomas and deregulation of P14/ARF (encoded by CDKN2A) seems to contribute to an MDM2-driven inactivation of P53. Br J Cancer. 2015;112(5):883-90. http://dx.doi.org/10.1038/bjc.2015.27. PMid:25668009.
97. Vaslet CA, Messier NJ, Kane AB. Accelerated progression of asbestos-induced mesotheliomas in heterozygous p53+/- mice. Toxicol Sci. 2002;68(2):331-8. http://dx.doi.org/10.1093/toxsci/68.2.331. PMid:12151629.
98. Severson DT, De Rienzo A, Bueno R. Mesothelioma in the age of "Omics": before and after The Cancer Genome Atlas. J Thorac Cardiovasc Surg. 2020;160(4):1078-83.e2. http://dx.doi.org/10.1016/j.jtcvs.2020.02.141. PMid:32475501.
99. Hylebos M, Van Camp G, Van Meerbeeck JP, Op de Beeck K. The genetic landscape of malignant pleural mesothelioma: results from massively parallel sequencing. J Thorac Oncol. 2016;11(10):1615-26. http://dx.doi.org/10.1016/j.jtho.2016.05.020. PMid:27282309.
100. Bueno R, de Rienzo A, Dong L, Gordon GJ, Hercus CF, Richards WG, et al. Second generation sequencing of the mesothelioma tumor genome. PLoS One. 2010;5(5):e10612. http://dx.doi.org/10.1371/journal.pone.0010612. PMid:20485525.
101. Shukuya T, Serizawa M, Watanabe M, Akamatsu H, Abe M, Imai H, et al. Identification of actionable mutations in malignant pleural mesothelioma. Lung Cancer. 2014;86(1):35-40. http://dx.doi.org/10.1016/j.lungcan.2014.08.004. PMid:25174276.
102. IARC: International Agency for Research on Cancer. IARC monographs on the evaluation of carcionogenic risks to humans. Lyon: WHO Press; 2012. Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite and Anthophyllite); p. 92.
103. Carbone M, Ly BH, Dodson RF, Pagano I, Morris PT, Dogan UA, et al. Malignant mesothelioma: facts, myths, and hypotheses. J Cell Physiol. 2012;227(1):44-58. http://dx.doi.org/10.1002/jcp.22724. PMid:21412769.
104. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer. 2013;13(3):153-9. http://dx.doi.org/10.1038/nrc3459. PMid:23550303.
105. Ventii KH, Devi NS, Friedrich KL, Chernova TA, Tighiouart M, Van Meir EG, et al. BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization. Cancer Res. 2008;68(17):6953-62. http://dx.doi.org/10.1158/0008-5472.CAN-08-0365. PMid:18757409.
106. Fang Y, Fu D, Shen X-Z. The potential role of ubiquitin c-terminal hydrolases in oncogenesis. Biochim Biophys Acta. 2010;1806(1):1-6. PMid:20302916.
107. Lund-Andersen C, Nakken S, Nygård S, Fromm B, Aasheim LB, Davidson B, et al. Integrative genomic analysis of peritoneal malignant mesothelioma: understanding a case with extraordinary chemotherapy response. Cold Spring Harb Mol Case Stud. 2019;5(2):1-15. http://dx.doi.org/10.1101/mcs.a003566. PMid:30862609.
108. Cheung M, Testa JR. BAP1, a tumor suppressor gene driving malignant mesothelioma. Transl Lung Cancer Res. 2017;6(3):270-8. http://dx.doi.org/10.21037/tlcr.2017.05.03. PMid:28713672.
109. Joseph NM, Chen YY, Nasr A, Yeh I, Talevich E, Onodera C, et al. Genomic profiling of malignant peritoneal mesothelioma reveals recurrent alterations in epigenetic regulatory genes BAP1, SETD2, and DDX3X. Mod Pathol. 2017;30(2):246-54. http://dx.doi.org/10.1038/modpathol.2016.188. PMid:27813512.
110. Luchini C, Veronese N, Yachida S, Cheng L, Nottegar A, Stubbs B, et al. Different prognostic roles of tumor suppressor gene BAP1 in cancer: A systematic review with meta-analysis. Genes Chromosomes Cancer. 2016;55(10):741-9. http://dx.doi.org/10.1002/gcc.22381. PMid:27223342.
111. Haugh AM, Njauw C-N, Bubley JA, Verzi AE, Zhang B, Kudalkar E, et al. Genotypic and phenotypic features of BAP1 cancer syndrome: a report of 8 new families and review of cases in the literature. JAMA Dermatol. 2017;153(10):999-1006. http://dx.doi.org/10.1001/jamadermatol.2017.2330. PMid:28793149.
112. Hanpude P, Bhattacharya S, Dey AK, Maiti TK. Deubiquitinating enzymes in cellular signaling and disease regulation. IUBMB Life. 2015;67(7):544-55. http://dx.doi.org/10.1002/iub.1402. PMid:26178252.
113. Hakiri S, Osada H, Ishiguro F, Murakami H, Murakami-tonami Y, Yokoi K, et al. Functional differences between wild-type and mutant-type BRCA1-associated protein 1 tumor suppressor against malignant mesothelioma cells. Cancer Sci. 2015;106(8):990-9. http://dx.doi.org/10.1111/cas.12698. PMid:26011428.
114. Wiesner T, Obenauf AC, Murali R, Fried I, Griewank KG, Ulz P, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011;43(10):1018-21. http://dx.doi.org/10.1038/ng.910. PMid:21874003.
115. Masoomian B, Shields JA, Shields CL. Overview of BAP1 cancer predisposition syndrome and the relationship to uveal melanoma. J Curr Ophthalmol. 2018;30(2):102-9. http://dx.doi.org/10.1016/j.joco.2018.02.005. PMid:29988936.
116. Baumann F, Flores E, Napolitano A, Kanodia S, Taioli E, Pass H, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis. 2015;36(1):76-81. http://dx.doi.org/10.1093/carcin/bgu227. PMid:25380601.
117. Ohar JA, Cheung M, Talarchek J, Howard SE, Howard TD, Hesdorffer M, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. Cancer

Res. 2016;76(2):206-15. http://dx.doi.org/10.1158/0008-5472.CAN-15-0295. PMid:26719535.

118. Betti M, Casalone E, Ferrante D, Aspesi A, Morleo G, Biasi A, et al. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. Cancer Lett. 2017;405:38-45. http://dx.doi.org/10.1016/j.canlet.2017.06.028. PMid:28687356.
119. Gordon GJ, Rockwell GN, Jensen RV, Rheinwald JG, Glickman JN, Aronson JP, et al. Identification of novel candidate oncogenes and tumor suppressors in malignant pleural mesothelioma using large-scale transcriptional profiling. Am J Pathol. 2005;166(6):1827-40. http://dx.doi.org/10.1016/S0002-9440(10)62492-3. PMid:15920167.
120. Hoang CD, D'Cunha J, Kratzke MG, Casmey CE, Frizelle SP, Maddaus MA, et al. . Gene expression profiling identifies matriptase overexpression in malignant mesothelioma. Chest. 2004;125(5):1843-52. http://dx.doi.org/10.1378/chest.125.5.1843. PMid:15136399.
121. Reyniès A, Jaurand MC, Renier A, Couchy G, Hysi I, Elarouci N, et al. Molecular classification of malignant pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res. 2014;20(5):1323-34. http://dx.doi.org/10.1158/1078-0432.CCR-13-2429. PMid:24443521.
122. Blum Y, Meiller C, Quetel L, Elarouci N, Ayadi M, Tashtanbaeva D, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. Nat Commun. 2019;10(1):1333. http://dx.doi.org/10.1038/s41467-019-09307-6. PMid:30902996.
123. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol. 1998;16(1):145-52. http://dx.doi.org/10.1200/JCO.1998.16.1.145. PMid:9440736.
124. Herndon JE 2nd, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest. 1998;113(3):723-31. http://dx.doi.org/10.1378/chest.113.3.723. PMid:9515850.
125. Brims FJH, Meniawy TM, Duffus I, De Fonseka D, Segal A, Creaney J, et al. A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. J Thorac Oncol. 2016;11(4):573-82. http://dx.doi.org/10.1016/j.jtho.2015.12.108. PMid:26776867.
126. Pass HI, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Supplementary prognostic variables for pleural mesothelioma: A report from the IASLC staging committee. J Thorac Oncol. 2014;9(6):856-64. http://dx.doi.org/10.1097/JTO.0000000000000181. PMid:24807157.
127. De Perrot M, Feld R, Cho BCJ, Bezjak A, Anraku M, Burkes R, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol. 2009;27(9):1413-8. http://dx.doi.org/10.1200/JCO.2008.17.5604. PMid:19224855.
128. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 2014;384(9948):1118-27. http://dx.doi.org/10.1016/S0140-6736(14)60418-9. PMid:24942631.
129. Rusch VW, Piantadosi S, Holmes EC. The role of extrapleural pneumonectomy in malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 1991;102(1):1-9. http://dx.doi.org/10.1016/S0022-5223(19)36577-8. PMid:2072706.
130. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev. 2004;(1):CD002916. PMid:14973997.
131. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M, et al. Extrapleural pneumonectomy versus pleurectomy/ decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg. 2008;135(3):620-6.e3. http://dx.doi.org/10.1016/j.jtcvs.2007.10.054. PMid:18329481.
132. Treasure T, Lang-lazdunski L, Waller D, Bliss JMM, Tan C, Entwisle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. 2011;12(8):763-72. http://dx.doi.org/10.1016/S1470-2045(11)70149-8. PMid:21723781.
133. Gomez DR, Rimner A, Simone CB 2nd, Cho BCJ, de Perrot M, Adjei AA, et al. The use of radiation therapy for the treatment of malignant pleural mesothelioma: expert opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol. 2019;14(7):1172-83. http://dx.doi.org/10.1016/j.jtho.2019.03.030. PMid:31125736.
134. Thieke C, Nicolay NH, Sterzing F, Hoffmann H, Roeder F, Safi S, et al. Long-term results in malignant pleural mesothelioma treated with neoadjuvant chemotherapy, extrapleural pneumonectomy and intensity-modulated radiotherapy. Radiat Oncol. 2015;10(1):267. http://dx.doi.org/10.1186/s13014-015-0575-5. PMid:26715491.
135. Stahel RA, Riesterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. Lancet Oncol. 2015;16(16):1651-8. http://dx.doi.org/10.1016/S1470-2045(15)00208-9. PMid:26538423.
136. Trovo M, Relevant A, Polesel J, Muraro E, Barresi L, Drigo A, et al. Radical hemithoracic radiotherapy vs. palliative radiotherapy in non-metastatic malignant pleural mesothelioma: results from a phase III, randomized clinical trial. Int J Radiat Oncol Biol Phys. 2021;109(5):1368-76. http://dx.doi.org/10.1016/j.ijrobp.2020.11.057. PMid:33259933.
137. de Perrot M, Feld R, Leighl NB, Hope A, Waddell TK, Keshavjee S, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2016;151(2):468-73. http://dx.doi.org/10.1016/j.jtcvs.2015.09.129. PMid:26614413.
138. Rimner A, Zauderer MG, Gomez DR, Adusumilli PS, Parhar PK, Wu AJ, et al. Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma. J Clin Oncol. 2016;34(23):2761-8. http://dx.doi.org/10.1200/JCO.2016.67.2675. PMid:27325859.
139. Simone CB 2nd, Vapiwala N, Hampshire MK, Metz JM. Palliative care in the management of lung cancer: analgesic utilization and barriers to optimal pain management. J Opioid Manag. 2012;8(1):9-16. http://dx.doi.org/10.5055/jom.2012.0091. PMid:22479880.
140. Ellis P, Davies AM, Evans WK, Haynes AE, Lloyd NS. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. J Thorac Oncol. 2006;1(6):591-601. http://dx.doi.org/10.1016/S1556-0864(15)30366-X. PMid:17409924.
141. Campbell NP, Kindler HL. Update on malignant pleural mesothelioma. Semin Respir Crit Care Med. 2011;32(1):102-10. http://dx.doi.org/10.1055/s-0031-1272874. PMid:21500129.
142. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10026):1405-14. http://dx.doi.org/10.1016/S0140-6736(15)01238-6. PMid:26719230.
143. Tsao AS, Miao J, Wistuba II, Vogelzang NJ, Heymach JV, Fossella FV, et al. Phase II trial of cediranib in combination with cisplatin and pemetrexed in chemotherapy-naïve patients with unresectable malignant pleural mesothelioma (SWOG S0905). J Clin Oncol. 2019;37(28):2537-47. http://dx.doi.org/10.1200/JCO.19.00269. PMid:31386610.
144. Scagliotti GV, Gaafar R, Nowak AK, Nakano T, van Meerbeeck J, Popat S, et al. Nintedanib in combination with pemetrexed and cisplatin for chemotherapy-naive patients with advanced malignant pleural mesothelioma (LUME-Meso): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2019;7(7):569-80. http://dx.doi.org/10.1016/S2213-2600(19)30139-0. PMid:31103412.
145. Pagano M, Ceresoli GL, Zucali PA, Pasello G, Garassino MC, Grosso F, et al. Randomized phase II study on gemcitabine with or without ramucirumab as second-line treatment for advanced malignant pleural mesothelioma (MPM): results of Italian Rames Study. J Clin Oncol. 2020;38(15, Supl.):9004. http://dx.doi.org/10.1200/JCO.2020.38.15_suppl.9004.
146. Hassan R, Alley EW, Kindler HL, Antonia SJ, Jahan TM, Jacobs-Small M, et al. Antimesothelin vaccine CRS-207 plus chemotherapy as front-line treatment for malignant pleural mesothelioma (MPM). J Clin Oncol. 2014;32(15, Supl.):7532. http://dx.doi.org/10.1200/jco.2014.32.15_suppl.7532.
147. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013;137(5):647-67. http://dx.doi.org/10.5858/arpa.2012-0214-OA. PMid:22929121.
148. Chambers CA, Sullivan TJ, Truong T, Allison JP. Secondary but not primary T cell responses are enhanced in CTLA-4-deficient CD8+ T cells. Eur J Immunol. 1998;28(10):3137-43. http://dx.doi.org/10.1002/

(SICI)1521-4141(199810)28:10<3137::AID-IMMU3137>3.0.CO;2-X. PMid:9808182.

149. Bonelli MA, Fumarola C, La Monica S, Alfieri R. New therapeutic strategies for malignant pleural mesothelioma. Biochem Pharmacol. 2017;123:8-18. http://dx.doi.org/10.1016/j.bcp.2016.07.012. PMid:27431778.

150. Maio M, Scherpereel A, Calabrò L, Aerts J, Perez SC, Bearz A, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol. 2017;18(9):1261-73. http://dx.doi.org/10.1016/S1470-2045(17)30446-1. PMid:28729154.

151. Alley EW, Lopez J, Santoro A, Morosky A, Saraf S, Piperdi B, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol. 2017;18(5):623-30. http://dx.doi.org/10.1016/S1470-2045(17)30169-9. PMid:28291584.

152. Kindler H, Karrison T, Tan YHC, Rose B, Ahmad M, Strausand C, et al. Phase II Trial of Pembrolizumab in Patients with Malignant Mesothelioma (MM): Interim Analysis. Journal of Thoracic Oncology. 2017;12(1):293–294.

153. Quispel-Janssen J, Noort V, Vries JF, Zimmerman M, Lalezari F, Thunnissen E, et al. Programmed Death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. J Thorac Oncol. 2018;13(10):1569-76. http://dx.doi.org/10.1016/j.jtho.2018.05.038. PMid:29908324.

154. Okada M, Kijima T, Aoe K, Kato T, Fujimoto N, Nakagawa K, et al. Clinical efficacy and safety of nivolumab: results of a multicenter, open-label, single-arm, japanese phase ii study in Malignant Pleural Mesothelioma (MERIT). Clin Cancer Res. 2019;25(18):5485-92. http://dx.doi.org/10.1158/1078-0432.CCR-19-0103. PMid:31164373.

155. Hassan R, Thomas A, Nemunaitis JJ, Patel MR, Bennouna J, Chen FL, et al. Efficacy and safety of avelumab treatment in patients with advanced unresectable mesothelioma. JAMA Oncol. 2019;5(3):351-7. http://dx.doi.org/10.1001/jamaoncol.2018.5428. PMid:30605211.

156. Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Lancet Respir Med. 2018;6(6):451-60. http://dx.doi.org/10.1016/S2213-2600(18)30151-6. PMid:29773326.

157. Disselhorst MJ, Quispel-Janssen J, Lalezari F, Monkhorst K, de Vries JF, Noort V, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. Lancet Respir Med. 2019;7(3):260-70. http://dx.doi.org/10.1016/S2213-2600(18)30420-X. PMid:30660511.

158. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001;22(5):265-8. http://dx.doi.org/10.1016/S1471-4906(01)01888-9. PMid:11323285.

159. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000;192(7):1027-34. http://dx.doi.org/10.1084/jem.192.7.1027. PMid:11015443.

160. Calabrò L, Morra A, Fonsatti E, Cutaia O, Fazio C, Annesi D, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med. 2015;3(4):301-9. http://dx.doi.org/10.1016/S2213-2600(15)00092-2. PMid:25819643.

161. Combaz-Lair C, Galateau-Sallé F, McLeer-Florin A, Le Stang N, David-Boudet L, Duruisseaux M, et al. Immune biomarkers PD-1/PD-L1 and TLR3 in malignant pleural mesotheliomas. Hum Pathol. 2016;52:9-18. http://dx.doi.org/10.1016/j.humpath.2016.01.010. PMid:26980049.

162. Cedrés S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PLoS One. 2015;10(3):e0121071. http://dx.doi.org/10.1371/journal.pone.0121071. PMid:25774992.

163. Khanna S, Thomas A, Abate-Daga D, Zhang J, Morrow B, Steinberg SM, et al. Malignant mesothelioma effusions are infiltrated by CD3+ T cells highly expressing PD-L1 and the PD-L1+ tumor cells within these effusions are susceptible to ADCC by the anti-PD-L1 antibody avelumab. J Thorac Oncol. 2016;11(11):1993-2005. http://dx.doi.org/10.1016/j.jtho.2016.07.033. PMid:27544053.

164. Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Ann Oncol. 2020;31(12):1734-45. http://dx.doi.org/10.1016/j.annonc.2020.09.009. PMid:32976938.

165. Fennell DA, Casbard AC, Porter C, Rudd R, Lester JF, Nicolson M, et al. A randomized phase II trial of oral vinorelbine as second-line therapy for patients with malignant pleural mesothelioma. J Clin Oncol. 2021;39(15, Supl.):8507. http://dx.doi.org/10.1200/JCO.2021.39.15_suppl.8507.

166. Ceresoli GL, Zucali PA, Gianoncelli L, Lorenzi E, Santoro A. Second-line treatment for malignant pleural mesothelioma. Cancer Treat Rev. 2010;36(1):24-32. http://dx.doi.org/10.1016/j.ctrv.2009.09.003. PMid:19879055.

167. Sørensen JB, Sundstrøm S, Perell K, Thielsen AK. Pemetrexed as second-line treatment in malignant pleural mesothelioma after platinum-based first-line treatment. J Thorac Oncol. 2007;2(2):147-52. http://dx.doi.org/10.1097/JTO.0b013e31802f3813. PMid:17410031.

168. Jassem J, Ramlau R, Santoro A, Schuette W, Chemaissani A, Hong S, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol. 2008;26(10):1698-704. http://dx.doi.org/10.1200/JCO.2006.09.9887. PMid:18375898.

169. Buikhuisen WA, Hiddinga BI, Baas P, van Meerbeeck JP. Second line therapy in malignant pleural mesothelioma: a systematic review. Lung Cancer. 2015;89(3):223-31. http://dx.doi.org/10.1016/j.lungcan.2015.06.018. PMid:26162564.

170. Forde PM, Sun Z, Anagnostou V, Kindler HL, Purcell WT, Goulart BHL, et al. PrE0505: phase II multicenter study of anti-PD-L1, durvalumab, in combination with cisplatin and pemetrexed for the first-line treatment of unresectable malignant pleural mesothelioma (MPM): a PrECOG LLC study. J Clin Oncol. 2020;38(15, Supl.):9003. http://dx.doi.org/10.1200/JCO.2020.38.15_suppl.9003.

171. Nowak AK, Lesterhuis WJ, Kok PS, Brown C, Hughes BG, Karikios DJ, et al. Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in. Lancet Oncol. 2020;21(9):1213-23. http://dx.doi.org/10.1016/S1470-2045(20)30462-9. PMid:32888453.